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(54) Title: NOVEL G PROTEIN-COUPLED RECEPTORS

(57) Abstract: The present invention provides a gene encoding a G protein-coupled receptor termed nGPCR-x; constructs and recombinant host cells incorporating the genes; the nGPCR-x polypeptides encoded by the gene; antibodies to the nGPCR-x polypeptides; and methods of making and using all of the foregoing.

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# NOVEL G PROTEIN-COUPLED RECEPTORS

## CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority of Application Serial No. 60/184715, filed 2000 February 24; Serial No. 60/184,725, filed 2000 February 24; Serial No. 60/184,712, filed 2000 February 24; Serial No. 60/184,606, filed 2000 February 24; Serial No. 60/184,602, filed 2000 February 24; Serial No. 60/184,604, filed 2000 February 24; Serial No. 60/184822, filed 2000 February 24; Serial No. 60/184,710, filed 2000 February 24; Serial No. 60/184,689, filed 2000 February 24; Serial No. 60/184,690, filed 2000 February 24; Serial No. 60/184,716, filed 2000 February 24, each of which is hereby incorporated by reference in its entirety.

## FIELD OF THE INVENTION

The present invention relates generally to the fields of genetics and cellular and molecular biology. More particularly, the invention relates to novel G protein coupled receptors, to polynucleotides that encode such novel receptors, to reagents such as antibodies, probes, primers and kits comprising such antibodies, probes, primers related to the same, and to methods which use the novel G protein coupled receptors, polynucleotides or reagents.

## BACKGROUND OF THE INVENTION

The G protein-coupled receptors (GPCRs) form a vast superfamily of cell surface receptors which are characterized by an amino-terminal extracellular domain, a carboxyl-terminal intracellular domain, and a serpentine structure that passes through the cell membrane seven times. Hence, such receptors are sometimes also referred to as seven transmembrane (7TM) receptors. These seven transmembrane domains define three extracellular loops and three intracellular loops, in addition to the amino- and carboxy- terminal domains. The extracellular portions of the receptor have a role in recognizing and binding one or more extracellular binding partners (*e.g.*, ligands), whereas the intracellular portions have a role in recognizing and communicating with downstream molecules in the signal transduction cascade.

The G protein-coupled receptors bind a variety of ligands including calcium ions, hormones, chemokines, neuropeptides, neurotransmitters, nucleotides, lipids, odorants, and even photons, and are important in the normal (and sometimes the aberrant) function of many cell types. [See generally Strosberg, *Eur. J. Biochem.* 196:1-10 (1991) and Bohm *et al., Biochem J.* 322:1-18 (1997).] When a specific ligand binds to its corresponding receptor, the ligand typically stimulates the receptor to activate a specific heterotrimeric guanine-nucleotide-binding regulatory protein (G-protein) that is coupled to the intracellular portion of the receptor. The G

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protein in turn transmits a signal to an effector molecule within the cell, by either stimulating or inhibiting the activity of that effector molecule. These effector molecules include adenylate cyclase, phospholipases and ion channels. Adenylate cyclase and phospholipases are enzymes that are involved in the production of the second messenger molecules cAMP, inositol triphosphate and diacyglycerol. It is through this sequence of events that an extracellular ligand stimuli exerts intracellular changes through a G protein-coupled receptor. Each such receptor has its own characteristic primary structure, expression pattern, ligand-binding profile, and intracellular effector system.

Because of the vital role of G protein-coupled receptors in the communication between cells and their environment, such receptors are attractive targets for therapeutic intervention, for example by activating or antagonizing such receptors. For receptors having a known ligand, the identification of agonists or antagonists may be sought specifically to enhance or inhibit the action of the ligand. Some G protein-coupled receptors have roles in disease pathogenesis (*e.g.*, certain chemokine receptors that act as HIV co-receptors may have a role in AIDS pathogenesis), and are attractive targets for therapeutic intervention even in the absence of knowledge of the natural ligand of the receptor. Other receptors are attractive targets for therapeutic intervention by virtue of their expression pattern in tissues or cell types that are themselves attractive targets for therapeutic intervention. Examples of this latter category of receptors include receptors expressed in immune cells, which can be targeted to either inhibit autoimmune responses or to enhance immune responses to fight pathogens or cancer; and receptors expressed in the brain or other neural organs and tissues, which are likely targets in the treatment of mental disorder, depression, bipolar disease, or other neurological disorders. This latter category of receptor is also useful as a marker for identifying and/or purifying (*e.g.*, via fluorescence-activated cell sorting) cellular subtypes that express the receptor. Unfortunately, only a limited number of G protein receptors from the central nervous system (CNS) are known. Thus, a need exists for G protein-coupled receptors that have been identified and show promise as targets for therapeutic intervention in a variety of animals, including humans.

## SUMMARY OF THE INVENTION

The present invention relates to an isolated nucleic acid molecule that comprises a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence homologous to sequences selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220, or a fragment thereof. The nucleic acid molecule encodes at least a portion of nGPCR-x. In some embodiments, the nucleic acid molecule comprises a sequence that encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:111 to SEQ ID



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NO:220, or a fragment thereof. In some embodiments, the nucleic acid molecule comprises a sequence homologous to a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110, or a fragment thereof. In some embodiments, the nucleic acid molecule comprises a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110, and fragments thereof.

According to some embodiments, the present invention provides vectors which comprise the nucleic acid molecule of the invention. In some embodiments, the vector is an expression vector.

According to some embodiments, the present invention provides host cells which comprise the vectors of the invention. In some embodiments, the host cells comprise expression vectors.

The present invention provides an isolated nucleic acid molecule comprising a nucleotide sequence complementary to at least a portion of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110, said portion comprising at least 10 nucleotides.

The present invention provides a method of producing a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220, or a homolog or fragment thereof. The method comprising the steps of introducing a recombinant expression vector that includes a nucleotide sequence that encodes the polypeptide into a compatible host cell, growing the host cell under conditions for expression of the polypeptide and recovering the polypeptide.

The present invention provides an isolated antibody which binds to an epitope on a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220, or a homolog or fragment thereof.

The present invention provides an method of inducing an immune response in a mammal against a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220, or a homolog or fragment thereof. The method comprises administering to a mammal an amount of the polypeptide sufficient to induce said immune response.

The present invention provides a method for identifying a compound which binds nGPCR-x. The method comprises the steps of contacting nGPCR-x with a compound and determining whether the compound binds nGPCR-x.

The present invention provides a method for identifying a compound which binds a nucleic acid molecule encoding nGPCR-x. The method comprises the steps of contacting said nucleic acid molecule encoding nGPCR-x with a compound and determining whether said compound binds said nucleic acid molecule.



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The present invention provides a method for identifying a compound which modulates the activity of nGPCR-x. The method comprises the steps of contacting nGPCR-x with a compound and determining whether nGPCR-x activity has been modulated.

The present invention provides a method of identifying an animal homolog of nGPCR-x. The method comprises the steps screening a nucleic acid database of the animal with a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110, or a portion thereof and determining whether a portion of said library or database is homologous to said sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110, or portion thereof.

The present invention provides a method of identifying an animal homolog of nGPCR-x. The methods comprises the steps screening a nucleic acid library of the animal with a nucleic acid molecule having a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110, or a portion thereof; and determining whether a portion of said library or database is homologous to said sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110, or a portion thereof.

Another aspect of the present invention relates to methods of screening a human subject to diagnose a disorder affecting the brain or genetic predisposition therefor. The methods comprise the steps of assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering an amino acid sequence, expression, or biological activity of at least one nGPCR-x that is expressed in the brain. The nGPCR-x comprise an amino acid sequence selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220, and allelic variants thereof. A diagnosis of the disorder or predisposition is made from the presence or absence of the mutation. The presence of a mutation altering the amino acid sequence, expression, or biological activity of the nGPCR-x in the nucleic acid correlates with an increased risk of developing the disorder.

The present invention further relates to methods of screening for a nGPCR-x hereditary mental disorder genotype in a human patient. The methods comprise the steps of providing a biological sample comprising nucleic acid from the patient, in which the nucleic acid includes sequences corresponding to alleles of nGPCR-x. The presence of one or more mutations in the nGPCR-x allele is indicative of a hereditary mental disorder genotype.

The present invention provides kits for screening a human subject to diagnose mental disorder or a genetic predisposition therefor. The kits include an oligonucleotide useful as a probe for identifying polymorphisms in a human nGPCR-x gene. The oligonucleotide comprises 6-50 nucleotides in a sequence that is identical or complementary to a sequence of a wild type human nGPCR-x gene sequence or nGPCR-x coding sequence, except for one sequence difference selected from the group consisting of a nucleotide addition, a nucleotide



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deletion, or nucleotide substitution. The kit also includes a media packaged with the oligonucleotide. The media contains information for identifying polymorphisms that correlate with mental disorder or a genetic predisposition therefor, the polymorphisms being identifiable using the oligonucleotide as a probe.

The present invention further relates to methods of identifying nGPCR-x allelic variants that correlates with mental disorders. The methods comprise the steps of providing biological samples that comprise nucleic acid from a human patient diagnosed with a mental disorder, or from the patient's genetic progenitors or progeny, and detecting in the nucleic acid the presence of one or more mutations in an nGPCR-x that is expressed in the brain. The nGPCR-x comprises an amino acid sequence selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220, and allelic variants thereof. The nucleic acid includes sequences corresponding to the gene or genes encoding nGPCR-x. The one or more mutations detected indicate an allelic variant that correlates with a mental disorder.

The present invention further relates to purified polynucleotides comprising nucleotide sequences encoding alleles of nGPCR-x from a human with mental disorder. The polynucleotide hybridizes to the complement of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110 under the following hybridization conditions: (a) hybridization for 16 hours at 42°C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaC1, 10% dextran sulfate and (b) washing 2 times for 30 minutes at 60°C in a wash solution comprising 0.1x SSC and 1% SDS. The polynucleotide that encodes nGPCR-x amino acid sequence of the human differs from a sequence selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220 by at least one residue.

The present invention also provides methods for identifying a modulator of biological activity of nGPCR-x comprising the steps of contacting a cell that expresses nGPCR-x in the presence and in the absence of a putative modulator compound and measuring nGPCR-x biological activity in the cell. The decreased or increased nGPCR-x biological activity in the presence versus absence of the putative modulator is indicative of a modulator of biological activity.

The present invention further provides methods to identify compounds useful for the treatment of mental disorders. The methods comprise the steps of contacting a composition comprising nGPCR-x with a compound suspected of binding nGPCR-x. The binding between nGPCR-x and the compound suspected of binding nGPCR-x is detected. Compounds identified as binding nGPCR-x are candidate compounds useful for the treatment of mental disorder. Compounds identified as binding nGPCR-x may be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity.



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The present invention further provides methods for identifying a compound useful as a modulator of binding between nGPCR-x and a binding partner of nGPCR-x. The methods comprise the steps of contacting the binding partner and a composition comprising nGPCR-x in the presence and in the absence of a putative modulator compound and detecting binding between the binding partner and nGPCR-x. Decreased or increased binding between the binding partner and nGPCR-x in the presence of the putative modulator, as compared to binding in the absence of the putative modulator is indicative a modulator compound useful for the treatment of a related disease or disorder. Compounds identified as modulating binding between nGPCR-x and a nGPCR-x binding partner may be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity as modulators.

Another aspect of the present invention relates to methods of purifying a G protein from a sample containing a G protein. The methods comprise the steps of contacting the sample with an nGPCR-x for a time sufficient to allow the G protein to form a complex with the nGPCR-x; isolating the complex from remaining components of the sample; maintaining the complex under conditions which result in dissociation of the G protein from the nGPCR-x; and isolating said G protein from the nGPCR-x.

## DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

### Definitions

Various definitions are made throughout this document. Most words have the meaning that would be attributed to those words by one skilled in the art. Words specifically defined either below or elsewhere in this document have the meaning provided in the context of the present invention as a whole and as are typically understood by those skilled in the art.

"Synthesized" as used herein and understood in the art, refers to polynucleotides produced by purely chemical, as opposed to enzymatic, methods. "Wholly" synthesized DNA sequences are therefore produced entirely by chemical means, and "partially" synthesized DNAs embrace those wherein only portions of the resulting DNA were produced by chemical means.

By the term "region" is meant a physically contiguous portion of the primary structure of a biomolecule. In the case of proteins, a region is defined by a contiguous portion of the amino acid sequence of that protein.

The term "domain" is herein defined as referring to a structural part of a biomolecule that contributes to a known or suspected function of the biomolecule. Domains may be co-extensive with regions or portions thereof; domains may also incorporate a portion of a biomolecule that is distinct from a particular region, in addition to all or part of that region . Examples of GPCR protein domains include, but are not limited to, the extracellular (*i.e.*, N-



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terminal), transmembrane and cytoplasmic (*i.e.*, C-terminal) domains, which are co-extensive with like-named regions of GPCRs; each of the seven transmembrane segments of a GPCR; and each of the loop segments (both extracellular and intracellular loops) connecting adjacent transmembrane segments.

As used herein, the term "activity" refers to a variety of measurable indicia suggesting or revealing binding, either direct or indirect; affecting a response, i.e. having a measurable affect in response to some exposure or stimulus, including, for example, the affinity of a compound for directly binding a polypeptide or polynucleotide of the invention, or, for example, measurement of amounts of upstream or downstream proteins or other similar functions after some stimulus or event.

Unless indicated otherwise, as used herein, the abbreviation in lower case (gpcr) refers to a gene, cDNA, RNA or nucleic acid sequence, while the upper case version (GPCR) refers to a protein, polypeptide, peptide, oligopeptide, or amino acid sequence. The term "nGPCR-x" refers to any of the nGPCRs taught herein, while specific reference to a nGPCR (for example nGPCR-2073) refers only to that specific nGPCR.

As used herein, the term "antibody" is meant to refer to complete, intact antibodies, and Fab, Fab', F(ab)2, and other fragments thereof. Complete, intact antibodies include monoclonal antibodies such as murine monoclonal antibodies, chimeric antibodies and humanized antibodies.

As used herein, the term "binding" means the physical or chemical interaction between two proteins or compounds or associated proteins or compounds or combinations thereof. Binding includes ionic, non-ionic, Hydrogen bonds, Van der Waals, hydrophobic interactions, etc. The physical interaction, the binding, can be either direct or indirect, indirect being through or due to the effects of another protein or compound. Direct binding refers to interactions that do not take place through or due to the effect of another protein or compound but instead are without other substantial chemical intermediates. Binding may be detected in many different manners. As a non-limiting example, the physical binding interaction between a nGPCR-x of the invention and a compound can be detected using a labeled compound. Alternatively, functional evidence of binding can be detected using, for example, a cell transfected with and expressing a nGPCR-x of the invention. Binding of the transfected cell to a ligand of the nGPCR-x that was transfected into the cell provides functional evidence of binding. Other methods of detecting binding are well known to those of skill in the art.

As used herein, the term "compound" means any identifiable chemical or molecule, including, but not limited to, small molecule, peptide, protein, sugar, nucleotide, or nucleic acid, and such compound can be natural or synthetic.



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As used herein, the term "complementary" refers to Watson-Crick basepairing between nucleotide units of a nucleic acid molecule.

As used herein, the term "contacting" means bringing together, either directly or indirectly, a compound into physical proximity to a polypeptide or polynucleotide of the invention. The polypeptide or polynucleotide can be in any number of buffers, salts, solutions *etc.* Contacting includes, for example, placing the compound into a beaker, microtiter plate, cell culture flask, or a microarray, such as a gene chip, or the like, which contains the nucleic acid molecule, or polypeptide encoding the nGPCR or fragment thereof.

As used herein, the phrase "homologous nucleotide sequence," or "homologous amino acid sequence," or variations thereof, refers to sequences characterized by a homology, at the nucleotide level or amino acid level, of at least the specified percentage. Homologous nucleotide sequences include those sequences coding for isoforms of proteins. Such isoforms can be expressed in different tissues of the same organism as a result of, for example, alternative splicing of RNA. Alternatively, isoforms can be encoded by different genes. Homologous nucleotide sequences include nucleotide sequences encoding for a protein of a species other than humans, including, but not limited to, mammals. Homologous nucleotide sequences also include, but are not limited to, naturally occurring allelic variations and mutations of the nucleotide sequences set forth herein. A homologous nucleotide sequence does not, however, include the nucleotide sequence encoding other known GPCRs. Homologous amino acid sequences include those amino acid sequences which contain conservative amino acid substitutions and which polypeptides have the same binding and/or activity. A homologous amino acid sequence does not, however, include the amino acid sequence encoding other known GPCRs. Percent homology can be determined by, for example, the Gap program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, Madison WI), using the default settings, which uses the algorithm of Smith and Waterman (Adv. Appl. Math., 1981, 2, 482-489, which is incorporated herein by reference in its entirety).

As used herein, the term "isolated" nucleic acid molecule refers to a nucleic acid molecule (DNA or RNA) that has been removed from its native environment. Examples of isolated nucleic acid molecules include, but are not limited to, recombinant DNA molecules contained in a vector, recombinant DNA molecules maintained in a heterologous host cell, partially or substantially purified nucleic acid molecules, and synthetic DNA or RNA molecules.

As used herein, the terms "modulates" or "modifies" means an increase or decrease in the amount, quality, or effect of a particular activity or protein.



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As used herein, the term "oligonucleotide" refers to a series of linked nucleotide residues which has a sufficient number of bases to be used in a polymerase chain reaction (PCR). This short sequence is based on (or designed from) a genomic or cDNA sequence and is used to amplify, confirm, or reveal the presence of an identical, similar or complementary DNA or RNA in a particular cell or tissue. Oligonucleotides comprise portions of a DNA sequence having at least about 10 nucleotides and as many as about 50 nucleotides, preferably about 15 to 30 nucleotides. They are chemically synthesized and may be used as probes.

As used herein, the term "probe" refers to nucleic acid sequences of variable length, preferably between at least about 10 and as many as about 6,000 nucleotides, depending on use. They are used in the detection of identical, similar, or complementary nucleic acid sequences. Longer length probes are usually obtained from a natural or recombinant source, are highly specific and much slower to hybridize than oligomers. They may be single- or double-stranded and carefully designed to have specificity in PCR, hybridization membrane-based, or ELISA-like technologies.

The term "preventing" refers to decreasing the probability that an organism contracts or develops an abnormal condition.

The term "treating" refers to having a therapeutic effect and at least partially alleviating or abrogating an abnormal condition in the organism.

The term "therapeutic effect" refers to the inhibition or activation factors causing or contributing to the abnormal condition. A therapeutic effect relieves to some extent one or more of the symptoms of the abnormal condition. In reference to the treatment of abnormal conditions, a therapeutic effect can refer to one or more of the following: (a) an increase in the proliferation, growth, and/or differentiation of cells; (b) inhibition (*i.e.*, slowing or stopping) of cell death; (c) inhibition of degeneration; (d) relieving to some extent one or more of the symptoms associated with the abnormal condition; and (e) enhancing the function of the affected population of cells. Compounds demonstrating efficacy against abnormal conditions can be identified as described herein.

The term "abnormal condition" refers to a function in the cells or tissues of an organism that deviates from their normal functions in that organism. An abnormal condition can relate to cell proliferation, cell differentiation, cell signaling, or cell survival. An abnormal condition may also include obesity, diabetic complications such as retinal degeneration, and irregularities in glucose uptake and metabolism, and fatty acid uptake and metabolism.

Abnormal cell proliferative conditions include cancers such as fibrotic and mesangial disorders, abnormal angiogenesis and vasculogenesis, wound healing, psoriasis, diabetes mellitus, and inflammation.



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Abnormal differentiation conditions include, but are not limited to, neurodegenerative disorders, slow wound healing rates, and slow tissue grafting healing rates. Abnormal cell signaling conditions include, but are not limited to, psychiatric disorders involving excess neurotransmitter activity.

Abnormal cell survival conditions may also relate to conditions in which programmed cell death (apoptosis) pathways are activated or abrogated. A number of protein kinases are associated with the apoptosis pathways. Aberrations in the function of any one of the protein kinases could lead to cell immortality or premature cell death.

The term "administering" relates to a method of incorporating a compound into cells or tissues of an organism. The abnormal condition can be prevented or treated when the cells or tissues of the organism exist within the organism or outside of the organism. Cells existing outside the organism can be maintained or grown in cell culture dishes. For cells harbored within the organism, many techniques exist in the art to administer compounds, including (but not limited to) oral, parenteral, dermal, injection, and aerosol applications. For cells outside of the organism, multiple techniques exist in the art to administer the compounds, including (but not limited to) cell microinjection techniques, transformation techniques and carrier techniques.

The abnormal condition can also be prevented or treated by administering a compound to a group of cells having an aberration in a signal transduction pathway to an organism. The effect of administering a compound on organism function can then be monitored. The organism is preferably a mouse, rat, rabbit, guinea pig or goat, more preferably a monkey or ape, and most preferably a human.

By "amplification" it is meant increased numbers of DNA or RNA in a cell compared with normal cells. "Amplification" as it refers to RNA can be the detectable presence of RNA in cells, since in some normal cells there is no basal expression of RNA. In other normal cells, a basal level of expression exists, therefore in these cases amplification is the detection of at least 1 to 2-fold, and preferably more, compared to the basal level.

As used herein, the phrase "stringent hybridization conditions" or "stringent conditions" refers to conditions under which a probe, primer, or oligonucleotide will hybridize to its target sequence, but to no other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures. Generally, stringent conditions are selected to be about 5°C lower than the thermal melting point ($T_m$) for the specific sequence at a defined ionic strength and pH. The $T_m$ is the temperature (under defined ionic strength, pH and nucleic acid concentration) at which 50% of the probes complementary to the target sequence hybridize to the target sequence at equilibrium. Since the target sequences are generally present in excess, at $T_m$, 50% of the



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probes are occupied at equilibrium. Typically, stringent conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes, primers or oligonucleotides (e.g. 10 to 50 nucleotides) and at least about 60°C for longer probes, primers or oligonucleotides. Stringent conditions may also be achieved with the addition of destabilizing agents, such as formamide.

The amino acid sequences are presented in the amino to carboxy direction, from left to right. The amino and carboxy groups are not presented in the sequence. The nucleotide sequences are presented by single strand only, in the 5' to 3' direction, from left to right. Nucleotides and amino acids are represented in the manner recommended by the IUPAC-IUB Biochemical Nomenclature Commission or (for amino acids) by three letters code.

**Polynucleotides**

The present invention provides purified and isolated polynucleotides (*e.g.*, DNA sequences and RNA transcripts, both sense and complementary antisense strands, both single- and double-stranded, including splice variants thereof) that encode unknown G protein-coupled receptors heretofore termed novel GPCRs, or nGPCRs. These genes are described herein and designated herein collectively as nGPCR-x (where x is 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, and 2140). Table 1 below identifies the novel gene sequence nGPCR-x designation, the SEQ ID NO: of the gene sequence, the SEQ ID NO: of the polypeptide encoded thereby, and the U.S. Provisional Application in which the gene sequence has been disclosed.

**Table 1**

| nGPCR | Nucleotide Sequence (SEQ ID NO:) | Amino acid Sequence (SEQ ID NO:) | Originally filed in: | | nGPCR | Nucleotide Sequence (SEQ ID NO:) | Amino acid Sequence (SEQ ID NO:) | Originally filed in: |
|---|---|---|---|---|---|---|---|---|
| 2031 | 1 | 111 | A | | 2086 | 56 | 166 | F |
| 2032 | 2 | 112 | A | | 2087 | 57 | 167 | F |
| 2033 | 3 | 113 | A | | 2088 | 58 | 168 | F |
| 2034 | 4 | 114 | A | | 2089 | 59 | 169 | F |
| 2035 | 5 | 115 | A | | 2090 | 60 | 170 | F |
| 2036 | 6 | 116 | A | | 2091 | 61 | 171 | G |
| 2037 | 7 | 117 | A | | 2092 | 62 | 172 | G |
| 2038 | 8 | 118 | A | | 2093 | 63 | 173 | G |
| 2039 | 9 | 119 | A | | 2094 | 64 | 174 | G |



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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 2040 | 10 | 120 | A | | 2095 | 65 | 175 | G |
| 2041 | 11 | 121 | B | | 2096 | 66 | 176 | G |
| 2042 | 12 | 122 | B | | 2097 | 67 | 177 | G |
| 2043 | 13 | 123 | B | | 2098 | 68 | 178 | G |
| 2044 | 14 | 124 | B | | 2099 | 69 | 179 | G |
| 2045 | 15 | 125 | B | | 2100 | 70 | 180 | G |
| 2046 | 16 | 126 | B | | 2101 | 71 | 181 | H |
| 2047 | 17 | 127 | B | | 2102 | 72 | 182 | H |
| 2048 | 18 | 128 | B | | 2103 | 73 | 183 | H |
| 2049 | 19 | 129 | B | | 2104 | 74 | 184 | H |
| 2050 | 20 | 130 | B | | 2105 | 75 | 185 | H |
| 2051 | 21 | 131 | C | | 2106 | 76 | 186 | H |
| 2052 | 22 | 132 | C | | 2107 | 77 | 187 | H |
| 2053 | 23 | 133 | C | | 2108 | 78 | 188 | H |
| 2054 | 24 | 134 | C | | 2109 | 79 | 189 | H |
| 2055 | 25 | 135 | C | | 2110 | 80 | 190 | H |
| 2056 | 26 | 136 | C | | 2111 | 81 | 191 | I |
| 2057 | 27 | 137 | C | | 2112 | 82 | 192 | I |
| 2058 | 28 | 138 | C | | 2113 | 83 | 193 | I |
| 2059 | 29 | 139 | C | | 2114 | 84 | 194 | I |
| 2060 | 30 | 140 | C | | 2115 | 85 | 195 | I |
| 2061 | 31 | 141 | D | | 2116 | 86 | 196 | I |
| 2062 | 32 | 142 | D | | 2117 | 87 | 197 | I |
| 2063 | 33 | 143 | D | | 2118 | 88 | 198 | I |
| 2064 | 34 | 144 | D | | 2119 | 89 | 199 | I |
| 2065 | 35 | 145 | D | | 2120 | 90 | 200 | I |
| 2066 | 36 | 146 | D | | 2121 | 91 | 201 | J |
| 2067 | 37 | 147 | D | | 2122 | 92 | 202 | J |
| 2068 | 38 | 148 | D | | 2123 | 93 | 203 | J |
| 2069 | 39 | 149 | D | | 2124 | 94 | 204 | J |
| 2070 | 40 | 150 | D | | 2125 | 95 | 205 | J |
| 2071 | 41 | 151 | E | | 2126 | 96 | 206 | J |
| 2072 | 42 | 152 | E | | 2127 | 97 | 207 | J |
| 2073 | 43 | 153 | E | | 2128 | 98 | 208 | J |
| 2074 | 44 | 154 | E | | 2129 | 99 | 209 | J |
| 2075 | 45 | 155 | E | | 2130 | 100 | 210 | J |
| 2076 | 46 | 156 | E | | 2131 | 101 | 211 | K |
| 2077 | 47 | 157 | E | | 2132 | 102 | 212 | K |
| 2078 | 48 | 158 | E | | 2133 | 103 | 213 | K |
| 2079 | 49 | 159 | E | | 2134 | 104 | 214 | K |
| 2080 | 50 | 160 | E | | 2135 | 105 | 215 | K |
| 2081 | 51 | 161 | F | | 2136 | 106 | 216 | K |
| 2082 | 52 | 162 | F | | 2137 | 107 | 217 | K |
| 2083 | 53 | 163 | F | | 2138 | 108 | 218 | K |
| 2084 | 54 | 164 | F | | 2139 | 109 | 219 | K |
| 2085 | 55 | 165 | F | | 2140 | 110 | 220 | K |

**Legend**

A= Ser. No. 60/184,715
C= Ser. No. 60/184,712
E= Ser. No. 60/184,602
G= Ser. No. 60/184,822
I= Ser. No. 60/184,689
K= Ser. No. 60/184,716

B= Ser. No. 60/184,725
D= Ser. No. 60/184,606
F= Ser. No. 60/184,604
H= Ser. No. 60/184,710
J= Ser. No. 60/184,690

When a specific nGPCR is identified (for example nGPCR-2085), it is understood that only that specific nGPCR is being referred to.

It is well known that GCPRs are expressed in many different tissues, including the brain. Accordingly, the nGPCR-x of the present invention may be useful, *inter alia*, for treating and/or diagnosing mental disorders. Following the techniques described in Example 5, below,



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those skilled in the art could readily ascertain if nGPCR-x is expressed in a particular tissue or region.

The invention provides purified and isolated polynucleotides (*e.g.*, cDNA, genomic DNA, synthetic DNA, RNA, or combinations thereof, whether single- or double-stranded) that comprise a nucleotide sequence encoding the amino acid sequence of the polypeptides of the invention. Such polynucleotides are useful for recombinantly expressing the receptor and also for detecting expression of the receptor in cells (*e.g.*, using Northern hybridization and *in situ* hybridization assays). Such polynucleotides also are useful in the design of antisense and other molecules for the suppression of the expression of nGPCR-x in a cultured cell, a tissue, or an animal; for therapeutic purposes; or to provide a model for diseases or conditions characterized by aberrant nGPCR-x expression. Specifically excluded from the definition of polynucleotides of the invention are entire isolated, non-recombinant native chromosomes of host cells. A preferred polynucleotide has a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110, which correspond to naturally occurring nGPCR-x sequences. It will be appreciated that numerous other polynucleotide sequences exist that also encode nGPCR-x having the sequence selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220, due to the well-known degeneracy of the universal genetic code.

The invention also provides a purified and isolated polynucleotide comprising a nucleotide sequence that encodes a mammalian polypeptide, wherein the polynucleotide hybridizes to a polynucleotide having the sequence set forth in sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110, or the non-coding strand complementary thereto, under the following hybridization conditions:

(a) hybridization for 16 hours at 42°C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% dextran sulfate; and

(b) washing 2 times for 30 minutes each at 60°C in a wash solution comprising 0.1% SSC, 1% SDS. Polynucleotides that encode a human allelic variant are highly preferred.

The present invention relates to molecules which comprise the gene sequences that encode the nGPCRs; constructs and recombinant host cells incorporating the gene sequences; the novel GPCR polypeptides encoded by the gene sequences; antibodies to the polypeptides and homologs; kits employing the polynucleotides and polypeptides, and methods of making and using all of the foregoing. In addition, the present invention relates to homologs of the gene sequences and of the polypeptides and methods of making and using the same.

Genomic DNA of the invention comprises the protein-coding region for a polypeptide of the invention and is also intended to include allelic variants thereof. It is widely understood that, for many genes, genomic DNA is transcribed into RNA transcripts that undergo one or



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more splicing events wherein intron (*i.e.*, non-coding regions) of the transcripts are removed, or "spliced out." RNA transcripts that can be spliced by alternative mechanisms, and therefore be subject to removal of different RNA sequences but still encode a nGPCR-x polypeptide, are referred to in the art as splice variants which are embraced by the invention. Splice variants comprehended by the invention therefore are encoded by the same original genomic DNA sequences but arise from distinct mRNA transcripts. Allelic variants are modified forms of a wild-type gene sequence, the modification resulting from recombination during chromosomal segregation or exposure to conditions which give rise to genetic mutation. Allelic variants, like wild type genes, are naturally occurring sequences (as opposed to non-naturally occurring variants that arise from *in vitro* manipulation).

The invention also comprehends cDNA that is obtained through reverse transcription of an RNA polynucleotide encoding nGPCR-x (conventionally followed by second strand synthesis of a complementary strand to provide a double-stranded DNA).

Preferred DNA sequences encoding human nGPCR-x polypeptides are selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110. A preferred DNA of the invention comprises a double stranded molecule along with the complementary molecule (the "non-coding strand" or "complement") having a sequence unambiguously deducible from the coding strand according to Watson-Crick base-pairing rules for DNA. Also preferred are other polynucleotides encoding the nGPCR-x polypeptide selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220, which differ in sequence from the polynucleotides selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110, by virtue of the well-known degeneracy of the universal nuclear genetic code.

The invention further embraces other species, preferably mammalian, homologs of the human nGPCR-x DNA. Species homologs, sometimes referred to as "orthologs," in general, share at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% homology with human DNA of the invention. Generally, percent sequence "homology" with respect to polynucleotides of the invention may be calculated as the percentage of nucleotide bases in the candidate sequence that are identical to nucleotides in the nGPCR-x sequence set forth in sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity.

Polynucleotides of the invention permit identification and isolation of polynucleotides encoding related nGPCR-x polypeptides, such as human allelic variants and species homologs, by well-known techniques including Southern and/or Northern hybridization, and polymerase



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chain reaction (PCR). Examples of related polynucleotides include human and non-human genomic sequences, including allelic variants, as well as polynucleotides encoding polypeptides homologous to nGPCR-x and structurally related polypeptides sharing one or more biological, immunological, and/or physical properties of nGPCR-x. Non-human species genes encoding proteins homologous to nGPCR-x can also be identified by Southern and/or PCR analysis and are useful in animal models for nGPCR-x disorders. Knowledge of the sequence of a human nGPCR-x DNA also makes possible through use of Southern hybridization or polymerase chain reaction (PCR) the identification of genomic DNA sequences encoding nGPCR-x expression control regulatory sequences such as promoters, operators, enhancers, repressors, and the like. Polynucleotides of the invention are also useful in hybridization assays to detect the capacity of cells to express nGPCR-x. Polynucleotides of the invention may also provide a basis for diagnostic methods useful for identifying a genetic alteration(s) in a nGPCR-x locus that underlies a disease state or states, which information is useful both for diagnosis and for selection of therapeutic strategies.

According to the present invention, the nGPCR-x nucleotide sequences disclosed herein may be used to identify homologs of the nGPCR-x, in other animals, including but not limited to humans and other mammals, and invertebrates. Any of the nucleotide sequences disclosed herein, or any portion thereof, can be used, for example, as probes to screen databases or nucleic acid libraries, such as, for example, genomic or cDNA libraries, to identify homologs, using screening procedures well known to those skilled in the art. Accordingly, homologs having at least 50%, more preferably at least 60%, more preferably at least 70%, more preferably at least 80%, more preferably at least 90%, more preferably at least 95%, and most preferably at least 100% homology with nGPCR-x sequences can be identified.

The disclosure herein of full-length polynucleotides encoding nGPCR-x polypeptides makes readily available to the worker of ordinary skill in the art every possible fragment of the full-length polynucleotide.

One preferred embodiment of the present invention provides an isolated nucleic acid molecule comprising a sequence homologous sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110, and fragments thereof. Another preferred embodiment provides an isolated nucleic acid molecule comprising a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110, and fragments thereof.

As used in the present invention, fragments of nGPCR-x-encoding polynucleotides comprise at least 10, and preferably at least 12, 14, 16, 18, 20, 25, 50, or 75 consecutive nucleotides of a polynucleotide encoding nGPCR-x. Preferably, fragment polynucleotides of the invention comprise sequences unique to the nGPCR-x-encoding polynucleotide sequence,



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and therefore hybridize under highly stringent or moderately stringent conditions only (*i.e.*, "specifically") to polynucleotides encoding nGPCR-x (or fragments thereof). Polynucleotide fragments of genomic sequences of the invention comprise not only sequences unique to the coding region, but also include fragments of the full-length sequence derived from introns, regulatory regions, and/or other non-translated sequences. Sequences unique to polynucleotides of the invention are recognizable through sequence comparison to other known polynucleotides, and can be identified through use of alignment programs routinely utilized in the art, *e.g.*, those made available in public sequence databases. Such sequences also are recognizable from Southern hybridization analyses to determine the number of fragments of genomic DNA to which a polynucleotide will hybridize. Polynucleotides of the invention can be labeled in a manner that permits their detection, including radioactive, fluorescent, and enzymatic labeling.

Fragment polynucleotides are particularly useful as probes for detection of full-length or fragments of nGPCR-x polynucleotides. One or more polynucleotides can be included in kits that are used to detect the presence of a polynucleotide encoding nGPCR-x, or used to detect variations in a polynucleotide sequence encoding nGPCR-x.

The invention also embraces DNAs encoding nGPCR-x polypeptides that hybridize under moderately stringent or high stringency conditions to the non-coding strand, or complement, of the polynucleotides set forth in sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110.

Exemplary highly stringent hybridization conditions are as follows: hybridization at 42°C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% Dextran sulfate, and washing twice for 30 minutes at 60°C in a wash solution comprising 0.1X SSC and 1% SDS. It is understood in the art that conditions of equivalent stringency can be achieved through variation of temperature and buffer, or salt concentration as described Ausubel *et al.* (Eds.), Protocols in Molecular Biology, John Wiley & Sons (1994), pp. 6.0.3 to 6.4.10. Modifications in hybridization conditions can be empirically determined or precisely calculated based on the length and the percentage of guanosine/cytosine (GC) base pairing of the probe. The hybridization conditions can be calculated as described in Sambrook, *et al.*, (Eds.), Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press: Cold Spring Harbor, New York (1989), pp. 9.47 to 9.51.

With the knowledge of the nucleotide sequence information disclosed in the present invention, one skilled in the art can identify and obtain nucleotide sequences which encode nGPCR-x from different sources (*i.e.*, different tissues or different organisms) through a variety of means well known to the skilled artisan and as disclosed by, for example, Sambrook et al.,



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"Molecular cloning: a laboratory manual", Second Edition, Cold Spring Harbor Press, Cold Spring Harbor, NY (1989), which is incorporated herein by reference in its entirety.

For example, DNA that encodes nGPCR-x may be obtained by screening of mRNA, cDNA, or genomic DNA with oligonucleotide probes generated from the nGPCR-x gene sequence information provided herein. Probes may be labeled with a detectable group, such as a fluorescent group, a radioactive atom or a chemiluminescent group in accordance with procedures known to the skilled artisan and used in conventional hybridization assays, as described by, for example, Sambrook *et al.*

A nucleic acid molecule comprising any of the nGPCR-x nucleotide sequences described above can alternatively be synthesized by use of the polymerase chain reaction (PCR) procedure, with the PCR oligonucleotide primers produced from the nucleotide sequences provided herein. See U.S. Patent Numbers 4,683,195 to Mullis *et al.* and 4,683,202 to Mullis. The PCR reaction provides a method for selectively increasing the concentration of a particular nucleic acid sequence even when that sequence has not been previously purified and is present only in a single copy in a particular sample. The method can be used to amplify either single- or double-stranded DNA. The essence of the method involves the use of two oligonucleotide probes to serve as primers for the template-dependent, polymerase mediated replication of a desired nucleic acid molecule.

A wide variety of alternative cloning and *in vitro* amplification methodologies are well known to those skilled in the art. Examples of these techniques are found in, for example, Berger *et al.*, *Guide to Molecular Cloning Techniques,* Methods in Enzymology 152, Academic Press, Inc., San Diego, CA (Berger), which is incorporated herein by reference in its entirety.

Automated sequencing methods can be used to obtain or verify the nucleotide sequence of nGPCR-x. The nGPCR-x nucleotide sequences of the present invention are believed to be 100% accurate. However, as is known in the art, nucleotide sequence obtained by automated methods may contain some errors. Nucleotide sequences determined by automation are typically at least about 90%, more typically at least about 95% to at least about 99.9% identical to the actual nucleotide sequence of a given nucleic acid molecule. The actual sequence may be more precisely determined using manual sequencing methods, which are well known in the art. An error in a sequence which results in an insertion or deletion of one or more nucleotides may result in a frame shift in translation such that the predicted amino acid sequence will differ from that which would be predicted from the actual nucleotide sequence of the nucleic acid molecule, starting at the point of the mutation.



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The nucleic acid molecules of the present invention, and fragments derived therefrom, are useful for screening for restriction fragment length polymorphism (RFLP) associated with certain disorders, as well as for genetic mapping.

The polynucleotide sequence information provided by the invention makes possible large-scale expression of the encoded polypeptide by techniques well known and routinely practiced in the art.

**Vectors**

Another aspect of the present invention is directed to vectors, or recombinant expression vectors, comprising any of the nucleic acid molecules described above. Vectors are used herein either to amplify DNA or RNA encoding nGPCR-x and/or to express DNA which encodes nGPCR-x. Preferred vectors include, but are not limited to, plasmids, phages, cosmids, episomes, viral particles or viruses, and integratable DNA fragments (*i.e.*, fragments integratable into the host genome by homologous recombination). Preferred viral particles include, but are not limited to, adenoviruses, baculoviruses, parvoviruses, herpesviruses, poxviruses, adeno-associated viruses, Semliki Forest viruses, vaccinia viruses, and retroviruses. Preferred expression vectors include, but are not limited to, pcDNA3 (Invitrogen) and pSVL (Pharmacia Biotech). Other expression vectors include, but are not limited to, pSPORT™ vectors, pGEM™ vectors (Promega), pPROEXvectors™ (LTI, Bethesda, MD), Bluescript™ vectors (Stratagene), pQE™ vectors (Qiagen), pSE420™ (Invitrogen), and pYES2™(Invitrogen).

Expression constructs preferably comprise GPCR-x-encoding polynucleotides operatively linked to an endogenous or exogenous expression control DNA sequence and a transcription terminator. Expression control DNA sequences include promoters, enhancers, operators, and regulatory element binding sites generally, and are typically selected based on the expression systems in which the expression construct is to be utilized. Preferred promoter and enhancer sequences are generally selected for the ability to increase gene expression, while operator sequences are generally selected for the ability to regulate gene expression. Expression constructs of the invention may also include sequences encoding one or more selectable markers that permit identification of host cells bearing the construct. Expression constructs may also include sequences that facilitate, and preferably promote, homologous recombination in a host cell. Preferred constructs of the invention also include sequences necessary for replication in a host cell.

Expression constructs are preferably utilized for production of an encoded protein, but may also be utilized simply to amplify a nGPCR-x-encoding polynucleotide sequence. In preferred embodiments, the vector is an expression vector wherein the polynucleotide of the invention is operatively linked to a polynucleotide comprising an expression control sequence.



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Autonomously replicating recombinant expression constructs such as plasmid and viral DNA vectors incorporating polynucleotides of the invention are also provided. Preferred expression vectors are replicable DNA constructs in which a DNA sequence encoding nGPCR-x is operably linked or connected to suitable control sequences capable of effecting the expression of the nGPCR-x in a suitable host. DNA regions are operably linked or connected when they are functionally related to each other. For example, a promoter is operably linked or connected to a coding sequence if it controls the transcription of the sequence. Amplification vectors do not require expression control domains, but rather need only the ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants. The need for control sequences in the expression vector will vary depending upon the host selected and the transformation method chosen. Generally, control sequences include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding and sequences which control the termination of transcription and translation.

Preferred vectors preferably contain a promoter that is recognized by the host organism. The promoter sequences of the present invention may be prokaryotic, eukaryotic or viral. Examples of suitable prokaryotic sequences include the $P_R$ and $P_L$ promoters of bacteriophage lambda (The bacteriophage Lambda, Hershey, A. D., Ed., Cold Spring Harbor Press, Cold Spring Harbor, NY (1973), which is incorporated herein by reference in its entirety; Lambda II, Hendrix, R. W., Ed., Cold Spring Harbor Press, Cold Spring Harbor, NY (1980), which is incorporated herein by reference in its entirety); the trp, recA, heat shock, and lacZ promoters of *E. coli* and the SV40 early promoter (Benoist *et al. Nature,* 1981, *290*, 304-310, which is incorporated herein by reference in its entirety). Additional promoters include, but are not limited to, mouse mammary tumor virus, long terminal repeat of human immunodeficiency virus, maloney virus, cytomegalovirus immediate early promoter, Epstein Barr virus, Rous sarcoma virus, human actin, human myosin, human hemoglobin, human muscle creatine, and human metalothionein.

Additional regulatory sequences can also be included in preferred vectors. Preferred examples of suitable regulatory sequences are represented by the Shine-Dalgarno of the replicase gene of the phage MS-2 and of the gene cII of bacteriophage lambda. The Shine-Dalgarno sequence may be directly followed by DNA encoding nGPCR-x and result in the expression of the mature nGPCR-x protein.

Moreover, suitable expression vectors can include an appropriate marker that allows the screening of the transformed host cells. The transformation of the selected host is carried out



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using any one of the various techniques well known to the expert in the art and described in Sambrook *et al., supra*.

An origin of replication can also be provided either by construction of the vector to include an exogenous origin or may be provided by the host cell chromosomal replication mechanism. If the vector is integrated into the host cell chromosome, the latter may be sufficient. Alternatively, rather than using vectors which contain viral origins of replication, one skilled in the art can transform mammalian cells by the method of co-transformation with a selectable marker and nGPCR-x DNA. An example of a suitable marker is dihydrofolate reductase (DHFR) or thymidine kinase (*see*, U.S. Patent No. 4,399,216).

Nucleotide sequences encoding GPCR-x may be recombined with vector DNA in accordance with conventional techniques, including blunt-ended or staggered-ended termini for ligation, restriction enzyme digestion to provide appropriate termini, filling in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesiderable joining, and ligation with appropriate ligases. Techniques for such manipulation are disclosed by Sambrook et al., *supra* and are well known in the art. Methods for construction of mammalian expression vectors are disclosed in, for example, Okayama *et al., Mol. Cell. Biol.*, **1983**, *3*, 280, Cosman *et al., Mol. Immunol.*, **1986**, *23*, 935, Cosman *et al., Nature*, **1984**, *312*, 768, EP-A-0367566, and WO 91/18982, each of which is incorporated herein by reference in its entirety.

**Host cells**

According to another aspect of the invention, host cells are provided, including prokaryotic and eukaryotic cells, comprising a polynucleotide of the invention (or vector of the invention) in a manner that permits expression of the encoded nGPCR-x polypeptide. Polynucleotides of the invention may be introduced into the host cell as part of a circular plasmid, or as linear DNA comprising an isolated protein coding region or a viral vector. Methods for introducing DNA into the host cell that are well known and routinely practiced in the art include transformation, transfection, electroporation, nuclear injection, or fusion with carriers such as liposomes, micelles, ghost cells, and protoplasts. Expression systems of the invention include bacterial, yeast, fungal, plant, insect, invertebrate, vertebrate, and mammalian cells systems.

The invention provides host cells that are transformed or transfected (stably or transiently) with polynucleotides of the invention or vectors of the invention. As stated above, such host cells are useful for amplifying the polynucleotides and also for expressing the nGPCR-x polypeptide or fragment thereof encoded by the polynucleotide.

In still another related embodiment, the invention provides a method for producing a nGPCR-x polypeptide (or fragment thereof) comprising the steps of growing a host cell of the



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invention in a nutrient medium and isolating the polypeptide or variant thereof from the cell or the medium. Because nGPCR-x is a seven transmembrane receptor, it will be appreciated that, for some applications, such as certain activity assays, the preferable isolation may involve isolation of cell membranes containing the polypeptide embedded therein, whereas for other applications a more complete isolation may be preferable.

According to some aspects of the present invention, transformed host cells having an expression vector comprising any of the nucleic acid molecules described above are provided. Expression of the nucleotide sequence occurs when the expression vector is introduced into an appropriate host cell. Suitable host cells for expression of the polypeptides of the invention include, but are not limited to, prokaryotes, yeast, and eukaryotes. If a prokaryotic expression vector is employed, then the appropriate host cell would be any prokaryotic cell capable of expressing the cloned sequences. Suitable prokaryotic cells include, but are not limited to, bacteria of the genera *Escherichia*, *Bacillus*, *Salmonella*, *Pseudomonas*, *Streptomyces*, and *Staphylococcus*.

If an eukaryotic expression vector is employed, then the appropriate host cell would be any eukaryotic cell capable of expressing the cloned sequence. Preferably, eukaryotic cells are cells of higher eukaryotes. Suitable eukaryotic cells include, but are not limited to, non-human mammalian tissue culture cells and human tissue culture cells. Preferred host cells include, but are not limited to, insect cells, HeLa cells, Chinese hamster ovary cells (CHO cells), African green monkey kidney cells (COS cells), human HEK-293 cells, and murine 3T3 fibroblasts. Propagation of such cells in cell culture has become a routine procedure (*see*, Tissue Culture, Academic Press, Kruse and Patterson, eds. (1973), which is incorporated herein by reference in its entirety).

In addition, a yeast host may be employed as a host cell. Preferred yeast cells include, but are not limited to, the genera *Saccharomyces*, *Pichia*, and *Kluveromyces*. Preferred yeast hosts are *S. cerevisiae* and *P. pastoris*. Preferred yeast vectors can contain an origin of replication sequence from a 2T yeast plasmid, an autonomously replication sequence (ARS), a promoter region, sequences for polyadenylation, sequences for transcription termination, and a selectable marker gene. Shuttle vectors for replication in both yeast and *E. coli* are also included herein.

Alternatively, insect cells may be used as host cells. In a preferred embodiment, the polypeptides of the invention are expressed using a baculovirus expression system (*see*, Luckow *et al.*, *Bio/Technology*, **1988**, *6*, 47, Baculovirus Expression Vectors: A Laboratory Manual, O'Rielly *et al.* (Eds.), W.H. Freeman and Company, New York, **1992**, and U.S. Patent No. 4,879,236, each of which is incorporated herein by reference in its entirety). In addition, the



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MAXBAC™ complete baculovirus expression system (Invitrogen) can, for example, be used for production in insect cells.

Host cells of the invention are a valuable source of immunogen for development of antibodies specifically immunoreactive with nGPCR-x. Host cells of the invention are also useful in methods for the large-scale production of nGPCR-x polypeptides wherein the cells are grown in a suitable culture medium and the desired polypeptide products are isolated from the cells, or from the medium in which the cells are grown, by purification methods known in the art, *e.g.,* conventional chromatographic methods including immunoaffinity chromatography, receptor affinity chromatography, hydrophobic interaction chromatography, lectin affinity chromatography, size exclusion filtration, cation or anion exchange chromatography, high pressure liquid chromatography (HPLC), reverse phase HPLC, and the like. Still other methods of purification include those methods wherein the desired protein is expressed and purified as a fusion protein having a specific tag, label, or chelating moiety that is recognized by a specific binding partner or agent. The purified protein can be cleaved to yield the desired protein, or can be left as an intact fusion protein. Cleavage of the fusion component may produce a form of the desired protein having additional amino acid residues as a result of the cleavage process.

Knowledge of nGPCR-x DNA sequences allows for modification of cells to permit, or increase, expression of endogenous nGPCR-x. Cells can be modified (*e.g.*, by homologous recombination) to provide increased expression by replacing, in whole or in part, the naturally occurring nGPCR-x promoter with all or part of a heterologous promoter so that the cells express nGPCR-x at higher levels. The heterologous promoter is inserted in such a manner that it is operatively linked to endogenous nGPCR-x encoding sequences. (See, for example, PCT International Publication No. WO 94/12650, PCT International Publication No. WO 92/20808, and PCT International Publication No. WO 91/09955.) It is also contemplated that, in addition to heterologous promoter DNA, amplifiable marker DNA (*e.g.*, ada, dhfr, and the multifunctional CAD gene which encodes carbamoyl phosphate synthase, aspartate transcarbamylase, and dihydroorotase) and/or intron DNA may be inserted along with the heterologous promoter DNA. If linked to the nGPCR-x coding sequence, amplification of the marker DNA by standard selection methods results in co-amplification of the nGPCR-x coding sequences in the cells.

**Knock-outs**

The DNA sequence information provided by the present invention also makes possible the development (*e.g.*, by homologous recombination or "knock-out" strategies; see Capecchi, *Science 244*:1288-1292 (1989), which is incorporated herein by reference) of animals that fail to express functional nGPCR-x or that express a variant of nGPCR-x. Such animals (especially



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small laboratory animals such as rats, rabbits, and mice) are useful as models for studying the *in vivo* activities of nGPCR-x and modulators of nGPCR-x.

**Antisense**

Also made available by the invention are anti-sense polynucleotides that recognize and hybridize to polynucleotides encoding nGPCR-x. Full-length and fragment anti-sense polynucleotides are provided. Fragment antisense molecules of the invention include (i) those that specifically recognize and hybridize to nGPCR-x RNA (as determined by sequence comparison of DNA encoding nGPCR-x to DNA encoding other known molecules). Identification of sequences unique to nGPCR-x encoding polynucleotides can be deduced through use of any publicly available sequence database, and/or through use of commercially available sequence comparison programs. After identification of the desired sequences, isolation through restriction digestion or amplification using any of the various polymerase chain reaction techniques well known in the art can be performed. Anti-sense polynucleotides are particularly relevant to regulating expression of nGPCR-x by those cells expressing nGPCR-x mRNA.

Antisense nucleic acids (preferably 10 to 30 base-pair oligonucleotides) capable of specifically binding to nGPCR-x expression control sequences or nGPCR-x RNA are introduced into cells (*e.g.*, by a viral vector or colloidal dispersion system such as a liposome). The antisense nucleic acid binds to the nGPCR-x target nucleotide sequence in the cell and prevents transcription and/or translation of the target sequence. Phosphorothioate and methylphosphonate antisense oligonucleotides are specifically contemplated for therapeutic use by the invention. The antisense oligonucleotides may be further modified by adding poly-L-lysine, transferrin polylysine, or cholesterol moieties at their 5' end. Suppression of nGPCR-x expression at either the transcriptional or translational level is useful to generate cellular or animal models for diseases/conditions characterized by aberrant nGPCR-x expression.

Antisense oligonucleotides, or fragments of sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110, or sequences complementary or homologous thereto, derived from the nucleotide sequences of the present invention encoding nGPCR-x are useful as diagnostic tools for probing gene expression in various tissues. For example, tissue can be probed *in situ* with oligonucleotide probes carrying detectable groups by conventional autoradiography techniques to investigate native expression of this enzyme or pathological conditions relating thereto. Antisense oligonucleotides are preferably directed to regulatory regions of sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110, or mRNA corresponding thereto, including, but not limited to, the initiation codon, TATA box, enhancer sequences, and the like.



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**Transcription factors**

The nGPCR-x sequences taught in the present invention facilitate the design of novel transcription factors for modulating nGPCR-x expression in native cells and animals, and cells transformed or transfected with nGPCR-x polynucleotides. For example, the $Cys_2$-$His_2$ zinc finger proteins, which bind DNA via their zinc finger domains, have been shown to be amenable to structural changes that lead to the recognition of different target sequences. These artificial zinc finger proteins recognize specific target sites with high affinity and low dissociation constants, and are able to act as gene switches to modulate gene expression. Knowledge of the particular nGPCR-x target sequence of the present invention facilitates the engineering of zinc finger proteins specific for the target sequence using known methods such as a combination of structure-based modeling and screening of phage display libraries (Segal *et al.*, Proc. Natl. Acad. Sci. (USA) 96:2758-2763 (1999); Liu *et al.*, Proc. Natl. Acad. Sci. (USA) 94:5525-5530 (1997); Greisman *et al.*, Science 275:657-661 (1997); Choo *et al.*, J. Mol. Biol. 273:525-532 (1997)). Each zinc finger domain usually recognizes three or more base pairs. Since a recognition sequence of 18 base pairs is generally sufficient in length to render it unique in any known genome, a zinc finger protein consisting of 6 tandem repeats of zinc fingers would be expected to ensure specificity for a particular sequence (Segal *et al.*) The artificial zinc finger repeats, designed based on nGPCR-x sequences, are fused to activation or repression domains to promote or suppress nGPCR-x expression (Liu *et al.)* Alternatively, the zinc finger domains can be fused to the TATA box-binding factor (TBP) with varying lengths of linker region between the zinc finger peptide and the TBP to create either transcriptional activators or repressors (Kim *et al.*, Proc. Natl. Acad. Sci. (USA) 94:3616-3620 (1997). Such proteins and polynucleotides that encode them, have utility for modulating nGPCR-x expression *in vivo* in both native cells, animals and humans; and/or cells transfected with nGPCR-x-encoding sequences. The novel transcription factor can be delivered to the target cells by transfecting constructs that express the transcription factor (gene therapy), or by introducing the protein. Engineered zinc finger proteins can also be designed to bind RNA sequences for use in therapeutics as alternatives to antisense or catalytic RNA methods (McColl *et al.*, Proc. Natl. Acad. Sci. (USA) 96:9521-9526 (1997); Wu *et al.*, Proc. Natl. Acad. Sci. (USA) 92:344-348 (1995)). The present invention contemplates methods of designing such transcription factors based on the gene sequence of the invention, as well as customized zinc finger proteins, that are useful to modulate nGPCR-x expression in cells (native or transformed) whose genetic complement includes these sequences.

**Polypeptides**

The invention also provides purified and isolated mammalian nGPCR-x polypeptides encoded by a polynucleotide of the invention. Presently preferred is a human nGPCR-x



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polypeptide comprising the amino acid sequence set out in sequences selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220, or fragments thereof comprising an epitope specific to the polypeptide. By "epitope specific to" is meant a portion of the nGPCR receptor that is recognizable by an antibody that is specific for the nGPCR, as defined in detail below.

Although the sequences provided are particular human sequences, the invention is intended to include within its scope other human allelic variants; non-human mammalian forms of nGPCR-x, and other vertebrate forms of nGPCR-x.

It will be appreciated that extracellular epitopes are particularly useful for generating and screening for antibodies and other binding compounds that bind to receptors such as nGPCR-x. Thus, in another preferred embodiment, the invention provides a purified and isolated polypeptide comprising at least one extracellular domain (*e.g.*, the N-terminal extracellular domain or one of the three extracellular loops) of nGPCR-x. Purified and isolated polypeptides comprising the N-terminal extracellular domain of nGPCR-x are highly preferred. Also preferred is a purified and isolated polypeptide comprising a nGPCR-x fragment selected from the group consisting of the N-terminal extracellular domain of nGPCR-x, transmembrane domains of nGPCR-x, an extracellular loop connecting transmembrane domains of nGPCR-x, an intracellular loop connecting transmembrane domains of nGPCR-x, the C-terminal cytoplasmic region of nGPCR-x, and fusions thereof. Such fragments may be continuous portions of the native receptor. However, it will also be appreciated that knowledge of the nGPCR-x gene and protein sequences as provided herein permits recombining of various domains that are not contiguous in the native protein. Using a FORTRAN computer program called "tmtrest.all" [Parodi *et al.*, Comput. Appl. Biosci. 5:527-535 (1994)], nGPCR-x was shown to contain transmembrane-spanning domains.

The invention also embraces polypeptides that have at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55% or at least 50% identity and/or homology to the preferred polypeptide of the invention. Percent amino acid sequence "identity" with respect to the preferred polypeptide of the invention is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the residues in the nGPCR-x sequence after aligning both sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Percent sequence "homology" with respect to the preferred polypeptide of the invention is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the residues in the nGPCR-x sequence after aligning the sequences and introducing gaps, if necessary, to



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achieve the maximum percent sequence identity, and also considering any conservative substitutions as part of the sequence identity.

In one aspect, percent homology is calculated as the percentage of amino acid residues in the smaller of two sequences which align with identical amino acid residue in the sequence being compared, when four gaps in a length of 100 amino acids may be introduced to maximize alignment (Dayhoff, in Atlas of Protein Sequence and Structure, Vol. 5, p. 124, National Biochemical Research Foundation, Washington, D.C. (1972), incorporated herein by reference).

Polypeptides of the invention may be isolated from natural cell sources or may be chemically synthesized, but are preferably produced by recombinant procedures involving host cells of the invention. Use of mammalian host cells is expected to provide for such post-translational modifications (*e.g.*, glycosylation, truncation, lipidation, and phosphorylation) as may be needed to confer optimal biological activity on recombinant expression products of the invention. Glycosylated and non-glycosylated forms of nGPCR-x polypeptides are embraced by the invention.

The invention also embraces variant (or analog) nGPCR-x polypeptides. In one example, insertion variants are provided wherein one or more amino acid residues supplement a nGPCR-x amino acid sequence. Insertions may be located at either or both termini of the protein, or may be positioned within internal regions of the nGPCR-x amino acid sequence. Insertional variants with additional residues at either or both termini can include, for example, fusion proteins and proteins including amino acid tags or labels.

Insertion variants include nGPCR-x polypeptides wherein one or more amino acid residues are added to a nGPCR-x acid sequence or to a biologically active fragment thereof.

Variant products of the invention also include mature nGPCR-x products, *i.e.*, nGPCR-x products wherein leader or signal sequences are removed, with additional amino terminal residues. The additional amino terminal residues may be derived from another protein, or may include one or more residues that are not identifiable as being derived from specific proteins. nGPCR-x products with an additional methionine residue at position -1 ($Met^{-1}$-nGPCR-x) are contemplated, as are variants with additional methionine and lysine residues at positions -2 and -1 ($Met^{-2}$-$Lys^{-1}$-nGPCR-x). Variants of nGPCR-x with additional Met, Met-Lys, Lys residues (or one or more basic residues in general) are particularly useful for enhanced recombinant protein production in bacterial host cells.

The invention also embraces nGPCR-x variants having additional amino acid residues that result from use of specific expression systems. For example, use of commercially available vectors that express a desired polypeptide as part of a glutathione-S-transferase (GST) fusion product provides the desired polypeptide having an additional glycine residue at position -1 after



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cleavage of the GST component from the desired polypeptide. Variants that result from expression in other vector systems are also contemplated.

Insertional variants also include fusion proteins wherein the amino terminus and/or the carboxy terminus of nGPCR-x is/are fused to another polypeptide.

In another aspect, the invention provides deletion variants wherein one or more amino acid residues in a nGPCR-x polypeptide are removed. Deletions can be effected at one or both termini of the nGPCR-x polypeptide, or with removal of one or more non-terminal amino acid residues of nGPCR-x. Deletion variants, therefore, include all fragments of a nGPCR-x polypeptide.

The invention also embraces polypeptide fragments of sequences selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220, wherein the fragments maintain biological (*e.g.*, ligand binding and/or intracellular signaling) immunological properties of a nGPCR-x polypeptide.

In one preferred embodiment of the invention, an isolated nucleic acid molecule comprises a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence homologous to sequences selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220, and fragments thereof, wherein the nucleic acid molecule encoding at least a portion of nGPCR-x. In a more preferred embodiment, the isolated nucleic acid molecule comprises a sequence that encodes a polypeptide comprising sequences selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220, and fragments thereof.

As used in the present invention, polypeptide fragments comprise at least 5, 10, 15, 20, 25, 30, 35, or 40 consecutive amino acids of sequences selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220. Preferred polypeptide fragments display antigenic properties unique to, or specific for, human nGPCR-x and its allelic and species homologs. Fragments of the invention having the desired biological and immunological properties can be prepared by any of the methods well known and routinely practiced in the art.

In still another aspect, the invention provides substitution variants of nGPCR-x polypeptides. Substitution variants include those polypeptides wherein one or more amino acid residues of a nGPCR-x polypeptide are removed and replaced with alternative residues. In one aspect, the substitutions are conservative in nature; however, the invention embraces substitutions that are also non-conservative. Conservative substitutions for this purpose may be defined as set out in Tables 2, 3, or 4 below.

Variant polypeptides include those wherein conservative substitutions have been introduced by modification of polynucleotides encoding polypeptides of the invention. Amino acids can be classified according to physical properties and contribution to secondary and



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tertiary protein structure. A conservative substitution is recognized in the art as a substitution of one amino acid for another amino acid that has similar properties. Exemplary conservative substitutions are set out in Table 2 (from WO 97/09433, page 10, published March 13, 1997 (PCT/GB96/02197, filed 9/6/96), immediately below.

**Table 2**

**Conservative Substitutions I**

| SIDE CHAIN CHARACTERISTIC | AMINO ACID |
|---|---|
| Aliphatic | |
| Non-polar | G A P |
| | I L V |
| Polar - uncharged | C S T M |
| | N Q |
| Polar - charged | D E |
| | K R |
| Aromatic | H F W Y |
| Other | N Q D E |

Alternatively, conservative amino acids can be grouped as described in Lehninger, [Biochemistry, Second Edition; Worth Publishers, Inc. NY, NY (1975), pp.71-77] as set out in Table 3, below.

**Table 3**
**Conservative Substitutions II**

| SIDE CHAIN CHARACTERISTIC | AMINO ACID |
|---|---|
| Non-polar (hydrophobic) | |
| A. Aliphatic: | A L I V P |
| B. Aromatic: | F W |
| C. Sulfur-containing: | M |
| D. Borderline: | G |
| Uncharged-polar | |
| A. Hydroxyl: | S T Y |
| B. Amides: | N Q |
| C. Sulfhydryl: | C |
| D. Borderline: | G |
| Positively Charged (Basic): | K R H |
| Negatively Charged (Acidic): | D E |

As still another alternative, exemplary conservative substitutions are set out in Table 4, below.

**Table 4**
**Conservative Substitutions III**

| Original Residue | Exemplary Substitution |
|---|---|
| Ala (A) | Val, Leu, Ile |
| Arg (R) | Lys, Gln, Asn |
| Asn (N) | Gln, His, Lys, Arg |
| Asp (D) | Glu |
| Cys (C) | Ser |
| Gln (Q) | Asn |



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| | |
|---|---|
| Glu (E) | Asp |
| His (H) | Asn, Gln, Lys, Arg |
| Ile (I) | Leu, Val, Met, Ala, Phe, |
| Leu (L) | Ile, Val, Met, Ala, Phe |
| Lys (K) | Arg, Gln, Asn |
| Met (M) | Leu, Phe, Ile |
| Phe (F) | Leu, Val, Ile, Ala |
| Pro (P) | Gly |
| Ser (S) | Thr |
| Thr (T) | Ser |
| Trp (W) | Tyr |
| Tyr (Y) | Trp, Phe, Thr, Ser |
| Val (V) | Ile, Leu, Met, Phe, Ala |

It should be understood that the definition of polypeptides of the invention is intended to include polypeptides bearing modifications other than insertion, deletion, or substitution of amino acid residues. By way of example, the modifications may be covalent in nature, and include for example, chemical bonding with polymers, lipids, other organic, and inorganic moieties. Such derivatives may be prepared to increase circulating half-life of a polypeptide, or may be designed to improve the targeting capacity of the polypeptide for desired cells, tissues, or organs. Similarly, the invention further embraces nGPCR-x polypeptides that have been covalently modified to include one or more water-soluble polymer attachments such as polyethylene glycol, polyoxyethylene glycol, or polypropylene glycol. Variants that display ligand binding properties of native nGPCR-x and are expressed at higher levels, as well as variants that provide for constitutively active receptors, are particularly useful in assays of the invention; the variants are also useful in providing cellular, tissue and animal models of diseases/conditions characterized by aberrant nGPCR-x activity.

In a related embodiment, the present invention provides compositions comprising purified polypeptides of the invention. Preferred compositions comprise, in addition to the polypeptide of the invention, a pharmaceutically acceptable (*i.e.,* sterile and non-toxic) liquid, semisolid, or solid diluent that serves as a pharmaceutical vehicle, excipient, or medium. Any diluent known in the art may be used. Exemplary diluents include, but are not limited to, water, saline solutions, polyoxyethylene sorbitan monolaurate, magnesium stearate, methyl- and propylhydroxybenzoate, talc, alginates, starches, lactose, sucrose, dextrose, sorbitol, mannitol, glycerol, calcium phosphate, mineral oil, and cocoa butter.

Variants that display ligand binding properties of native nGPCR-x and are expressed at higher levels, as well as variants that provide for constitutively active receptors, are particularly useful in assays of the invention; the variants are also useful in assays of the invention and in



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providing cellular, tissue and animal models of diseases/conditions characterized by aberrant nGPCR-x activity.

The G protein-coupled receptor functions through a specific heterotrimeric guanine-nucleotide-binding regulatory protein (G-protein) coupled to the intracellular portion of the G protein-coupled receptor molecule. Accordingly, the G protein-coupled receptor has a specific affinity to G protein. G proteins specifically bind to guanine nucleotides. Isolation of G proteins provides a means to isolate guanine nucleotides. G proteins may be isolated using commercially available anti-G protein antibodies or isolated G protein-coupled receptors. Similarly, G proteins may be detected in a sample isolated using commercially available detectable anti-G protein antibodies or isolated G protein-coupled receptors.

According to the present invention, the isolated nGPCR-x proteins of the present invention are useful to isolate and purify G proteins from samples such as cell lysates. Example 15 below sets forth an example of isolation of G proteins using isolated nGPCR-x proteins. Such methodolgy may be used in place of the use of commercially available anti-G protein antibodies which are used to isolate G proteins. Moreover, G proteins may be detected using n-GPCR-x proteins in place of commercially available detectable anti-G protein antibodies. Since nGPCR-x proteins specifically bind to G proteins, they can be employed in any specific use where G protein specific affinity is required such as those uses where commercially available anti-G protein antibodies are employed.

**Antibodies**

Also comprehended by the present invention are antibodies (*e.g.*, monoclonal and polyclonal antibodies, single chain antibodies, chimeric antibodies, bifunctional/bispecific antibodies, humanized antibodies, human antibodies, and complementary determining region (CDR)-grafted antibodies, including compounds which include CDR sequences which specifically recognize a polypeptide of the invention) specific for nGPCR-x or fragments thereof. Preferred antibodies of the invention are human antibodies that are produced and identified according to methods described in WO93/11236, published June 20, 1993, which is incorporated herein by reference in its entirety. Antibody fragments, including Fab, Fab′, $F(ab')_2$, and $F_v$, are also provided by the invention. The term "specific for," when used to describe antibodies of the invention, indicates that the variable regions of the antibodies of the invention recognize and bind nGPCR-x polypeptides exclusively (*i.e.*, are able to distinguish nGPCR-x polypeptides from other known GPCR polypeptides by virtue of measurable differences in binding affinity, despite the possible existence of localized sequence identity, homology, or similarity between nGPCR-x and such polypeptides). It will be understood that specific antibodies may also interact with other proteins (for example, *S. aureus* protein A or



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other antibodies in ELISA techniques) through interactions with sequences outside the variable region of the antibodies, and, in particular, in the constant region of the molecule. Screening assays to determine binding specificity of an antibody of the invention are well known and routinely practiced in the art. For a comprehensive discussion of such assays, see Harlow *et al.* (Eds.), Antibodies A Laboratory Manual; Cold Spring Harbor Laboratory; Cold Spring Harbor, NY (1988), Chapter 6. Antibodies that recognize and bind fragments of the nGPCR-x polypeptides of the invention are also contemplated, provided that the antibodies are specific for nGPCR-x polypeptides. Antibodies of the invention can be produced using any method well known and routinely practiced in the art.

The invention provides an antibody that is specific for the nGPCR-x of the invention. Antibody specificity is described in greater detail below. However, it should be emphasized that antibodies that can be generated from polypeptides that have previously been described in the literature and that are capable of fortuitously cross-reacting with nGPCR-x (*e.g.*, due to the fortuitous existence of a similar epitope in both polypeptides) are considered "cross-reactive" antibodies. Such cross-reactive antibodies are not antibodies that are "specific" for nGPCR-x. The determination of whether an antibody is specific for nGPCR-x or is cross-reactive with another known receptor is made using any of several assays, such as Western blotting assays, that are well known in the art. For identifying cells that express nGPCR-x and also for modulating nGPCR-x-ligand binding activity, antibodies that specifically bind to an extracellular epitope of the nGPCR-x are preferred.

In one preferred variation, the invention provides monoclonal antibodies. Hybridomas that produce such antibodies also are intended as aspects of the invention. In yet another variation, the invention provides a humanized antibody. Humanized antibodies are useful for *in vivo* therapeutic indications.

In another variation, the invention provides a cell-free composition comprising polyclonal antibodies, wherein at least one of the antibodies is an antibody of the invention specific for nGPCR-x. Antisera isolated from an animal is an exemplary composition, as is a composition comprising an antibody fraction of an antisera that has been resuspended in water or in another diluent, excipient, or carrier.

In still another related embodiment, the invention provides an anti-idiotypic antibody specific for an antibody that is specific for nGPCR-x.

It is well known that antibodies contain relatively small antigen binding domains that can be isolated chemically or by recombinant techniques. Such domains are useful nGPCR-x binding molecules themselves, and also may be reintroduced into human antibodies, or fused to toxins or other polypeptides. Thus, in still another embodiment, the invention provides a



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polypeptide comprising a fragment of a nGPCR-x-specific antibody, wherein the fragment and the polypeptide bind to the nGPCR-x. By way of non-limiting example, the invention provides polypeptides that are single chain antibodies and CDR-grafted antibodies.

Non-human antibodies may be humanized by any of the methods known in the art. In one method, the non-human CDRs are inserted into a human antibody or consensus antibody framework sequence. Further changes can then be introduced into the antibody framework to modulate affinity or immunogenicity.

Antibodies of the invention are useful for, *e.g.*, therapeutic purposes (by modulating activity of nGPCR-x), diagnostic purposes to detect or quantitate nGPCR-x, and purification of nGPCR-x. Kits comprising an antibody of the invention for any of the purposes described herein are also comprehended. In general, a kit of the invention also includes a control antigen for which the antibody is immunospecific.

**Compositions**

Mutations in the nGPCR-x gene that result in loss of normal function of the nGPCR-x gene product underlie nGPCR-x-related human disease states. The invention comprehends gene therapy to restore nGPCR-x activity to treat those disease states. Delivery of a functional nGPCR-x gene to appropriate cells is effected *ex vivo*, *in situ*, or *in vivo* by use of vectors, and more particularly viral vectors (*e.g.*, adenovirus, adeno-associated virus, or a retrovirus), or *ex vivo* by use of physical DNA transfer methods (*e.g.*, liposomes or chemical treatments). See, for example, Anderson, *Nature*, supplement to vol. 392, no. 6679, pp.25-20 (1998). For additional reviews of gene therapy technology see Friedmann, *Science, 244*: 1275-1281 (1989); Verma, *Scientific American*: 68-84 (1990); and Miller, *Nature, 357*: 455-460 (1992). Alternatively, it is contemplated that in other human disease states, preventing the expression of, or inhibiting the activity of, nGPCR-x will be useful in treating disease states. It is contemplated that antisense therapy or gene therapy could be applied to negatively regulate the expression of nGPCR-x.

Another aspect of the present invention is directed to compositions, including pharmaceutical compositions, comprising any of the nucleic acid molecules or recombinant expression vectors described above and an acceptable carrier or diluent. Preferably, the carrier or diluent is pharmaceutically acceptable. Suitable carriers are described in the most recent edition of *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in this field, which is incorporated herein by reference in its entirety. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Liposomes and nonaqueous vehicles such as fixed oils may also be used. The formulations are sterilized by commonly used techniques.



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Also within the scope of the invention are compositions comprising polypeptides, polynucleotides, or antibodies of the invention that have been formulated with, *e.g.*, a pharmaceutically acceptable carrier.

The invention also provides methods of using antibodies of the invention. For example, the invention provides a method for modulating ligand binding of a nGPCR-x comprising the step of contacting the nGPCR-x with an antibody specific for the nGPCR-x, under conditions wherein the antibody binds the receptor.

As discussed above, it is well known that GPCRs are expressed in many different tissues and regions, including in the brain. GPCRs that may be expressed in the brain, such as nGPCR-x, provide an indication that aberrant nGPCR-x signaling activity may correlate with one or more neurological or psychological disorders. The invention also provides a method for treating a neurological or psychiatric disorder comprising the step of administering to a mammal in need of such treatment an amount of an antibody-like polypeptide of the invention that is sufficient to modulate ligand binding to a nGPCR-x in neurons of the mammal. nGPCR-x may also be expressed in other tissues, including but not limited to, peripheral blood lymphocytes, pancreas, ovary, uterus, testis, salivary gland, thyroid gland, kidney, adrenal gland, liver, bone marrow, prostate, fetal liver, colon, muscle, and fetal brain, and may be found in many other tissues. Within the brain, nGPCR-x mRNA transcripts may be found in many tissues, including, but not limited to, frontal lobe, hypothalamus, pons, cerebellum, caudate nucleus, and medulla.

**Kits**

The present invention is also directed to kits, including pharmaceutical kits. The kits can comprise any of the nucleic acid molecules described above, any of the polypeptides described above, or any antibody which binds to a polypeptide of the invention as described above, as well as a negative control. The kit preferably comprises additional components, such as, for example, instructions, solid support, reagents helpful for quantification, and the like.

In another aspect, the invention features methods for detection of a polypeptide in a sample as a diagnostic tool for diseases or disorders, wherein the method comprises the steps of: (a) contacting the sample with a nucleic acid probe which hybridizes under hybridization assay conditions to a nucleic acid target region of a polypeptide having sequences selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220, said probe comprising the nucleic acid sequence encoding the polypeptide, fragments thereof, and the complements of the sequences and fragments; and (b) detecting the presence or amount of the probe:target region hybrid as an indication of the disease.

In preferred embodiments of the invention, the disease is selected from the group consisting of thyroid disorders (*e.g.* thyreotoxicosis, myxoedema); renal failure; inflammatory



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conditions (*e.g.*, Crohn's disease); diseases related to cell differentiation and homeostasis; rheumatoid arthritis; autoimmune disorders; movement disorders; CNS disorders (*e.g.*, pain including migraine; stroke; psychotic and neurological disorders, including anxiety, mental disorder, manic depression, anxiety, generalized anxiety disorder, post-traumatic-stress disorder, depression, bipolar disorder, delirium, dementia, severe mental retardation; dyskinesias, such as Huntington's disease or Tourette's Syndrome; attention disorders including ADD and ADHD, and degenerative disorders such as Parkinson's, Alzheimer's; movement disorders, including ataxias, supranuclear palsy, *etc.*); infections, such as viral infections caused by HIV-1 or HIV-2; metabolic and cardiovascular diseases and disorders (*e.g.*, type 2 diabetes, impaired glucose tolerance, dyslipidemia, obesity, anorexia, hypotension, hypertension, thrombosis, myocardial infarction, cardiomyopathies, atherosclerosis, *etc.*); proliferative diseases and cancers (*e.g.*, different cancers such as breast, colon, lung, *etc.*, and hyperproliferative disorders such as psoriasis, prostate hyperplasia, *etc.*); hormonal disorders (*e.g.*, male/female hormonal replacement, polycystic ovarian syndrome, alopecia, *etc.*); and sexual dysfunction, among others.

Kits may be designed to detect either expression of polynucleotides encoding nGPCR-x expressed in the brain or the nGPCR-x proteins themselves in order to identify tissue as being neurological. For example, oligonucleotide hybridization kits can be provided which include a container having an oligonucleotide probe specific for the nGPCR-x-specific DNA and optionally, containers with positive and negative controls and/or instructions. Similarly, PCR kits can be provided which include a container having primers specific for the nGPCR-x-specific sequences, DNA and optionally, containers with size markers, positive and negative controls and/or instructions.

Hybridization conditions should be such that hybridization occurs only with the genes in the presence of other nucleic acid molecules. Under stringent hybridization conditions only highly complementary nucleic acid sequences hybridize. Preferably, such conditions prevent hybridization of nucleic acids having 1 or 2 mismatches out of 20 contiguous nucleotides. Such conditions are defined supra.

The diseases for which detection of genes in a sample could be diagnostic include diseases in which nucleic acid (DNA and/or RNA) is amplified in comparison to normal cells. By "amplification" is meant increased numbers of DNA or RNA in a cell compared with normal cells.

The diseases that could be diagnosed by detection of nucleic acid in a sample preferably include central nervous system and metabolic diseases. The test samples suitable for nucleic acid probing methods of the present invention include, for example, cells or nucleic acid extracts



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of cells, or biological fluids. The samples used in the above-described methods will vary based on the assay format, the detection method and the nature of the tissues, cells or extracts to be assayed. Methods for preparing nucleic acid extracts of cells are well known in the art and can be readily adapted in order to obtain a sample that is compatible with the method utilized.

Alternatively, immunoassay kits can be provided which have containers container having antibodies specific for the nGPCR-x-protein and optionally, containers with positive and negative controls and/or instructions.

Kits may also be provided useful in the identification of GPCR binding partners such as natural ligands or modulators (agonists or antagonists). Substances useful for treatment of disorders or diseases preferably show positive results in one or more *in vitro* assays for an activity corresponding to treatment of the disease or disorder in question. Substances that modulate the activity of the polypeptides preferably include, but are not limited to, antisense oligonucleotides, agonists and antagonists, and inhibitors of protein kinases.

**Methods of inducing immune response**

Another aspect of the present invention is directed to methods of inducing an immune response in a mammal against a polypeptide of the invention by administering to the mammal an amount of the polypeptide sufficient to induce an immune response. The amount will be dependent on the animal species, size of the animal, and the like but can be determined by those skilled in the art.

**Methods of identifying ligands**

The invention also provides assays to identify compounds that bind nGPCR-x. One such assay comprises the steps of: (a) contacting a composition comprising a nGPCR-x with a compound suspected of binding nGPCR-x; and (b) measuring binding between the compound and nGPCR-x. In one variation, the composition comprises a cell expressing nGPCR-x on its surface. In another variation, isolated nGPCR-x or cell membranes comprising nGPCR-x are employed. The binding may be measured directly, *e.g.*, by using a labeled compound, or may be measured indirectly by several techniques, including measuring intracellular signaling of nGPCR-x induced by the compound (or measuring changes in the level of nGPCR-x signaling). Following steps (a) and (b), compounds identified as binding nGPCR-x may be tested in other assays including, but not limited to, *in vivo* models, to confirm or quantitate binding to nGPCR-x.

Specific binding molecules, including natural ligands and synthetic compounds, can be identified or developed using isolated or recombinant nGPCR-x products, nGPCR-x variants, or preferably, cells expressing such products. Binding partners are useful for purifying nGPCR-x products and detection or quantification of nGPCR-x products in fluid and tissue samples using



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known immunological procedures. Binding molecules are also manifestly useful in modulating (*i.e.*, blocking, inhibiting or stimulating) biological activities of nGPCR-x, especially those activities involved in signal transduction.

The DNA and amino acid sequence information provided by the present invention also makes possible identification of binding partner compounds with which a nGPCR-x polypeptide or polynucleotide will interact. Methods to identify binding partner compounds include solution assays, *in vitro* assays wherein nGPCR-x polypeptides are immobilized, and cell-based assays. Identification of binding partner compounds of nGPCR-x polypeptides provides candidates for therapeutic or prophylactic intervention in pathologies associated with nGPCR-x normal and aberrant biological activity.

The invention includes several assay systems for identifying nGPCR-x binding partners. In solution assays, methods of the invention comprise the steps of (a) contacting a nGPCR-x polypeptide with one or more candidate binding partner compounds and (b) identifying the compounds that bind to the nGPCR-x polypeptide. Identification of the compounds that bind the nGPCR-x polypeptide can be achieved by isolating the nGPCR-x polypeptide/binding partner complex, and separating the binding partner compound from the nGPCR-x polypeptide. An additional step of characterizing the physical, biological, and/or biochemical properties of the binding partner compound is also comprehended in another embodiment of the invention, wherein compounds identified as binding nGPCR-x may be tested in other assays including, but not limited to, *in vivo* models, to confirm or quantitate binding to nGPCR-x. In one aspect, the nGPCR-x polypeptide/binding partner complex is isolated using an antibody immunospecific for either the nGPCR-x polypeptide or the candidate binding partner compound.

In still other embodiments, either the nGPCR-x polypeptide or the candidate binding partner compound comprises a label or tag that facilitates its isolation, and methods of the invention to identify binding partner compounds include a step of isolating the nGPCR-x polypeptide/binding partner complex through interaction with the label or tag. An exemplary tag of this type is a poly-histidine sequence, generally around six histidine residues, that permits isolation of a compound so labeled using nickel chelation. Other labels and tags, such as the FLAG® tag (Eastman Kodak, Rochester, NY), well known and routinely used in the art, are embraced by the invention.

In one variation of an *in vitro* assay, the invention provides a method comprising the steps of (a) contacting an immobilized nGPCR-x polypeptide with a candidate binding partner compound and (b) detecting binding of the candidate compound to the nGPCR-x polypeptide. In an alternative embodiment, the candidate binding partner compound is immobilized and binding of nGPCR-x is detected. Immobilization is accomplished using any of the methods well



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known in the art, including covalent bonding to a support, a bead, or a chromatographic resin, as well as non-covalent, high affinity interactions such as antibody binding, or use of streptavidin/biotin binding wherein the immobilized compound includes a biotin moiety. Detection of binding can be accomplished (i) using a radioactive label on the compound that is not immobilized, (ii) using of a fluorescent label on the non-immobilized compound, (iii) using an antibody immunospecific for the non-immobilized compound, (iv) using a label on the non-immobilized compound that excites a fluorescent support to which the immobilized compound is attached, as well as other techniques well known and routinely practiced in the art.

The invention also provides cell-based assays to identify binding partner compounds of a nGPCR-x polypeptide. In one embodiment, the invention provides a method comprising the steps of contacting a nGPCR-x polypeptide expressed on the surface of a cell with a candidate binding partner compound and detecting binding of the candidate binding partner compound to the nGPCR-x polypeptide. In a preferred embodiment, the detection comprises detecting a calcium flux or other physiological event in the cell caused by the binding of the molecule.

Another aspect of the present invention is directed to methods of identifying compounds that bind to either nGPCR-x or nucleic acid molecules encoding nGPCR-x, comprising contacting nGPCR-x, or a nucleic acid molecule encoding the same, with a compound, and determining whether the compound binds nGPCR-x or a nucleic acid molecule encoding the same. Binding can be determined by binding assays which are well known to the skilled artisan, including, but not limited to, gel-shift assays, Western blots, radiolabeled competition assay, phage-based expression cloning, co-fractionation by chromatography, co-precipitation, cross linking, interaction trap/two-hybrid analysis, southwestern analysis, ELISA, and the like, which are described in, for example, *Current Protocols in Molecular Biology*, **1999**, John Wiley & Sons, NY, which is incorporated herein by reference in its entirety. The compounds to be screened include (which may include compounds which are suspected to bind nGPCR-x, or a nucleic acid molecule encoding the same), but are not limited to, extracellular, intracellular, biologic or chemical origin. The methods of the invention also embrace ligands, especially neuropeptides, that are attached to a label, such as a radiolabel (*e.g.*, $^{125}I$, $^{35}S$, $^{32}P$, $^{33}P$, $^{3}H$), a fluorescence label, a chemiluminescent label, an enzymic label and an immunogenic label. Modulators falling within the scope of the invention include, but are not limited to, non-peptide molecules such as non-peptide mimetics, non-peptide allosteric effectors, and peptides. The nGPCR-x polypeptide or polynucleotide employed in such a test may either be free in solution, attached to a solid support, borne on a cell surface or located intracellularly or associated with a portion of a cell. One skilled in the art can, for example, measure the formation of complexes between nGPCR-x and the compound being tested. Alternatively, one skilled in the art can



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examine the diminution in complex formation between nGPCR-x and its substrate caused by the compound being tested.

In another embodiment of the invention, high throughput screening for compounds having suitable binding affinity to nGPCR-x is employed. Briefly, large numbers of different test compounds are synthesized on a solid substrate. The peptide test compounds are contacted with nGPCR-x and washed. Bound nGPCR-x is then detected by methods well known in the art. Purified polypeptides of the invention can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the protein and immobilize it on the solid support.

Generally, an expressed nGPCR-x can be used for HTS binding assays in conjunction with its defined ligand, in this case the corresponding neuropeptide that activates it. The identified peptide is labeled with a suitable radioisotope, including, but not limited to, $^{125}I$, $^{3}H$, $^{35}S$ or $^{32}P$, by methods that are well known to those skilled in the art. Alternatively, the peptides may be labeled by well-known methods with a suitable fluorescent derivative (Baindur *et al.*, *Drug Dev. Res.*, **1994**, *33*, 373-398; Rogers, *Drug Discovery Today*, **1997**, *2*, 156-160). Radioactive ligand specifically bound to the receptor in membrane preparations made from the cell line expressing the recombinant protein can be detected in HTS assays in one of several standard ways, including filtration of the receptor-ligand complex to separate bound ligand from unbound ligand (Williams, *Med. Res. Rev.*, **1991**, *11*, 147-184; Sweetnam *et al.*, *J. Natural Products*, **1993**, *56*, 441-455). Alternative methods include a scintillation proximity assay (SPA) or a FlashPlate format in which such separation is unnecessary (Nakayama, *Cur. Opinion Drug Disc. Dev.*, **1998**, *1*, 85-91 Bossé *et al.*, *J. Biomolecular Screening*, **1998**, *3*, 285-292.). Binding of fluorescent ligands can be detected in various ways, including fluorescence energy transfer (FRET), direct spectrophotofluorometric analysis of bound ligand, or fluorescence polarization (Rogers, *Drug Discovery Today*, **1997**, *2*, 156-160; Hill, *Cur. Opinion* Drug Disc. *Dev.*, **1998**, *1*, 92-97).

Other assays may be used to identify specific ligands of a nGPCR-x receptor, including assays that identify ligands of the target protein through measuring direct binding of test ligands to the target protein, as well as assays that identify ligands of target proteins through affinity ultrafiltration with ion spray mass spectroscopy/HPLC methods or other physical and analytical methods. Alternatively, such binding interactions are evaluated indirectly using the yeast two-hybrid system described in Fields *et al.*, Nature, 340:245-246 (1989), and Fields *et al.*, Trends in Genetics, 10:286-292 (1994), both of which are incorporated herein by reference. The two-hybrid system is a genetic assay for detecting interactions between two proteins or polypeptides. It can be used to identify proteins that bind to a known protein of interest, or to delineate



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domains or residues critical for an interaction. Variations on this methodology have been developed to clone genes that encode DNA binding proteins, to identify peptides that bind to a protein, and to screen for drugs. The two-hybrid system exploits the ability of a pair of interacting proteins to bring a transcription activation domain into close proximity with a DNA binding domain that binds to an upstream activation sequence (UAS) of a reporter gene, and is generally performed in yeast. The assay requires the construction of two hybrid genes encoding (1) a DNA-binding domain that is fused to a first protein and (2) an activation domain fused to a second protein. The DNA-binding domain targets the first hybrid protein to the UAS of the reporter gene; however, because most proteins lack an activation domain, this DNA-binding hybrid protein does not activate transcription of the reporter gene. The second hybrid protein, which contains the activation domain, cannot by itself activate expression of the reporter gene because it does not bind the UAS. However, when both hybrid proteins are present, the noncovalent interaction of the first and second proteins tethers the activation domain to the UAS, activating transcription of the reporter gene. For example, when the first protein is a GPCR gene product, or fragment thereof, that is known to interact with another protein or nucleic acid, this assay can be used to detect agents that interfere with the binding interaction. Expression of the reporter gene is monitored as different test agents are added to the system. The presence of an inhibitory agent results in lack of a reporter signal.

The yeast two-hybrid assay can also be used to identify proteins that bind to the gene product. In an assay to identify proteins that bind to a nGPCR-x receptor, or fragment thereof, a fusion polynucleotide encoding both a nGPCR-x receptor (or fragment) and a UAS binding domain (*i.e.*, a first protein) may be used. In addition, a large number of hybrid genes each encoding a different second protein fused to an activation domain are produced and screened in the assay. Typically, the second protein is encoded by one or more members of a total cDNA or genomic DNA fusion library, with each second protein-coding region being fused to the activation domain. This system is applicable to a wide variety of proteins, and it is not even necessary to know the identity or function of the second binding protein. The system is highly sensitive and can detect interactions not revealed by other methods; even transient interactions may trigger transcription to produce a stable mRNA that can be repeatedly translated to yield the reporter protein.

Other assays may be used to search for agents that bind to the target protein. One such screening method to identify direct binding of test ligands to a target protein is described in U.S. Patent No. 5,585,277, incorporated herein by reference. This method relies on the principle that proteins generally exist as a mixture of folded and unfolded states, and continually alternate between the two states. When a test ligand binds to the folded form of a target protein (*i.e.*,



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when the test ligand is a ligand of the target protein), the target protein molecule bound by the ligand remains in its folded state. Thus, the folded target protein is present to a greater extent in the presence of a test ligand which binds the target protein, than in the absence of a ligand. Binding of the ligand to the target protein can be determined by any method that distinguishes between the folded and unfolded states of the target protein. The function of the target protein need not be known in order for this assay to be performed. Virtually any agent can be assessed by this method as a test ligand, including, but not limited to, metals, polypeptides, proteins, lipids, polysaccharides, polynucleotides and small organic molecules.

Another method for identifying ligands of a target protein is described in Wieboldt *et al.*, Anal. Chem., 69:1683-1691 (1997), incorporated herein by reference. This technique screens combinatorial libraries of 20-30 agents at a time in solution phase for binding to the target protein. Agents that bind to the target protein are separated from other library components by simple membrane washing. The specifically selected molecules that are retained on the filter are subsequently liberated from the target protein and analyzed by HPLC and pneumatically assisted electrospray (ion spray) ionization mass spectroscopy. This procedure selects library components with the greatest affinity for the target protein, and is particularly useful for small molecule libraries.

Other embodiments of the invention comprise using competitive screening assays in which neutralizing antibodies capable of binding a polypeptide of the invention specifically compete with a test compound for binding to the polypeptide. In this manner, the antibodies can be used to detect the presence of any peptide that shares one or more antigenic determinants with nGPCR-x. Radiolabeled competitive binding studies are described in A.H. Lin *et al.* *Antimicrobial Agents and Chemotherapy*, **1997**, vol. 41, no. 10. pp. 2127-2131, the disclosure of which is incorporated herein by reference in its entirety.

**Identification of modulating agents**

The invention also provides methods for identifying a modulator of binding between a nGPCR-x and a nGPCR-x binding partner, comprising the steps of: (a) contacting a nGPCR-x binding partner and a composition comprising a nGPCR-x in the presence and in the absence of a putative modulator compound; (b) detecting binding between the binding partner and the nGPCR-x; and (c) identifying a putative modulator compound or a modulator compound in view of decreased or increased binding between the binding partner and the nGPCR-x in the presence of the putative modulator, as compared to binding in the absence of the putative modulator. Following steps (a) and (b), compounds identified as modulating binding between nGPCR-x and a nGPCR-x binding partner may be tested in other assays including, but not limited to, *in vivo* models, to confirm or quantitate modulation of binding to nGPCR-x.



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nGPCR-x binding partners that stimulate nGPCR-x activity are useful as agonists in disease states or conditions characterized by insufficient nGPCR-x signaling (*e.g.*, as a result of insufficient activity of a nGPCR-x ligand). nGPCR-x binding partners that block ligand-mediated nGPCR-x signaling are useful as nGPCR-x antagonists to treat disease states or conditions characterized by excessive nGPCR-x signaling. In addition nGPCR-x modulators in general, as well as nGPCR-x polynucleotides and polypeptides, are useful in diagnostic assays for such diseases or conditions.

In another aspect, the invention provides methods for treating a disease or abnormal condition by administering to a patient in need of such treatment a substance that modulates the activity or expression of a polypeptide having sequences selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220.

Agents that modulate (*i.e.*, increase, decrease, or block) nGPCR-x activity or expression may be identified by incubating a putative modulator with a cell containing a nGPCR-x polypeptide or polynucleotide and determining the effect of the putative modulator on nGPCR-x activity or expression. The selectivity of a compound that modulates the activity of nGPCR-x can be evaluated by comparing its effects on nGPCR-x to its effect on other GPCR compounds. Following identification of compounds that modulate nGPCR-x activity or expression, such compounds may be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity. Selective modulators may include, for example, antibodies and other proteins, peptides, or organic molecules that specifically bind to a nGPCR-x polypeptide or a nGPCR-x-encoding nucleic acid. Modulators of nGPCR-x activity will be therapeutically useful in treatment of diseases and physiological conditions in which normal or aberrant nGPCR-x activity is involved. nGPCR-x polynucleotides, polypeptides, and modulators may be used in the treatment of such diseases and conditions as infections, such as viral infections caused by HIV-1 or HIV-2; pain; cancers; metabolic and cardiovascular diseases and disorders (*e.g.*, type 2 diabetes, impaired glucose tolerance, dyslipidemia, obesity, anorexia, hypotension, hypertension, thrombosis, myocardial infarction, cardiomyopathies, atherosclerosis, *etc.*); Parkinson's disease; and psychotic and neurological disorders, including schizophrenia, migraine, ADHH, major depression, anxiety, mental disorder, manic depression, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Tourette's Syndrome, among others. nGPCR-x polynucleotides and polypeptides, as well as nGPCR-x modulators, may also be used in diagnostic assays for such diseases or conditions.

Methods of the invention to identify modulators include variations on any of the methods described above to identify binding partner compounds, the variations including techniques wherein a binding partner compound has been identified and the binding assay is carried out in



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the presence and absence of a candidate modulator. A modulator is identified in those instances where binding between the nGPCR-x polypeptide and the binding partner compound changes in the presence of the candidate modulator compared to binding in the absence of the candidate modulator compound. A modulator that increases binding between the nGPCR-x polypeptide and the binding partner compound is described as an enhancer or activator, and a modulator that decreases binding between the nGPCR-x polypeptide and the binding partner compound is described as an inhibitor. Following identification of modulators, such compounds may be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity as modulators.

The invention also comprehends high-throughput screening (HTS) assays to identify compounds that interact with or inhibit biological activity (*i.e.*, affect enzymatic activity, binding activity, *etc.*) of a nGPCR-x polypeptide. HTS assays permit screening of large numbers of compounds in an efficient manner. Cell-based HTS systems are contemplated to investigate nGPCR-x receptor-ligand interaction. HTS assays are designed to identify "hits" or "lead compounds" having the desired property, from which modifications can be designed to improve the desired property. Chemical modification of the "hit" or "lead compound" is often based on an identifiable structure/activity relationship between the "hit" and the nGPCR-x polypeptide.

Another aspect of the present invention is directed to methods of identifying compounds which modulate (*i.e.*, increase or decrease) an activity of nGPCR-x comprising contacting nGPCR-x with a compound, and determining whether the compound modifies activity of nGPCR-x. The activity in the presence of the test compared is measured to the activity in the absence of the test compound. Where the activity of the sample containing the test compound is higher than the activity in the sample lacking the test compound, the compound will have increased activity. Similarly, where the activity of the sample containing the test compound is lower than the activity in the sample lacking the test compound, the compound will have inhibited activity. Following the identification of compounds that modulate an activity of nGPCR-x, such compounds can be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity.

The present invention is particularly useful for screening compounds by using nGPCR-x in any of a variety of drug screening techniques. The compounds to be screened include (which may include compounds which are suspected to modulate nGPCR-x activity), but are not limited to, extracellular, intracellular, biologic or chemical origin. The nGPCR-x polypeptide employed in such a test may be in any form, preferably, free in solution, attached to a solid support, borne on a cell surface or located intracellularly. One skilled in the art can, for example, measure the



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formation of complexes between nGPCR-x and the compound being tested. Alternatively, one skilled in the art can examine the diminution in complex formation between nGPCR-x and its substrate caused by the compound being tested.

The activity of nGPCR-x polypeptides of the invention can be determined by, for example, examining the ability to bind or be activated by chemically synthesized peptide ligands. Alternatively, the activity of nGPCR-x polypeptides can be assayed by examining their ability to bind calcium ions, hormones, chemokines, neuropeptides, neurotransmitters, nucleotides, lipids, odorants, and photons. Alternatively, the activity of the nGPCR-x polypeptides can be determined by examining the activity of effector molecules including, but not limited to, adenylate cyclase, phospholipases and ion channels. Thus, modulators of nGPCR-x polypeptide activity may alter a GPCR receptor function, such as a binding property of a receptor or an activity such as G protein-mediated signal transduction or membrane localization. In various embodiments of the method, the assay may take the form of an ion flux assay, a yeast growth assay, a non-hydrolyzable GTP assay such as a [$^{35}$S]-GTP $\gamma$S assay, a cAMP assay, an inositol triphosphate assay, a diacylglycerol assay, an Aequorin assay, a Luciferase assay, a FLIPR assay for intracellular $Ca^{2+}$ concentration, a mitogenesis assay, a MAP Kinase activity assay, an arachidonic acid release assay (*e.g.*, using [$^{3}$H]-arachidonic acid), and an assay for extracellular acidification rates, as well as other binding or function-based assays of nGPCR-x activity that are generally known in the art. In several of these embodiments, the invention comprehends the inclusion of any of the G proteins known in the art, such as $G_{16}$, $G_{15}$, or chimeric $G_{qd5}$ , $G_{qs5}$, $G_{qo5}$, $G_{q25}$, and the like. nGPCR-x activity can be determined by methodologies that are used to assay for FaRP activity, which is well known to those skilled in the art. Biological activities of nGPCR-x receptors according to the invention include, but are not limited to, the binding of a natural or an unnatural ligand, as well as any one of the functional activities of GPCRs known in the art. Non-limiting examples of GPCR activities include transmembrane signaling of various forms, which may involve G protein association and/or the exertion of an influence over G protein binding of various guanidylate nucleotides; another exemplary activity of GPCRs is the binding of accessory proteins or polypeptides that differ from known G proteins.

The modulators of the invention exhibit a variety of chemical structures, which can be generally grouped into non-peptide mimetics of natural GPCR receptor ligands, peptide and non-peptide allosteric effectors of GPCR receptors, and peptides that may function as activators or inhibitors (competitive, uncompetitive and non-competitive) (*e.g.*, antibody products) of GPCR receptors. The invention does not restrict the sources for suitable modulators, which may be obtained from natural sources such as plant, animal or mineral extracts, or non-natural



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sources such as small molecule libraries, including the products of combinatorial chemical approaches to library construction, and peptide libraries. Examples of peptide modulators of GPCR receptors exhibit the following primary structures: GLGPRPLRFamide, GNSFLRFamide, GGPQGPLRFamide, GPSGPLRFamide, PDVDHVFLRFamide, and pyro-EDVDHVFLRFamide.

Other assays can be used to examine enzymatic activity including, but not limited to, photometric, radiometric, HPLC, electrochemical, and the like, which are described in, for example, *Enzyme Assays: A Practical Approach*, eds. R. Eisenthal and M. J. Danson, **1992**, Oxford University Press, which is incorporated herein by reference in its entirety.

The use of cDNAs encoding GPCRs in drug discovery programs is well-known; assays capable of testing thousands of unknown compounds per day in high-throughput screens (HTSs) are thoroughly documented. The literature is replete with examples of the use of radiolabeled ligands in HTS binding assays for drug discovery (see Williams, M*edicinal Research Reviews*, **1991**, *11*, 147-184.; Sweetnam, *et al.*, *J. Natural Products*, **1993**, *56*, 441-455 for review). Recombinant receptors are preferred for binding assay HTS because they allow for better specificity (higher relative purity), provide the ability to generate large amounts of receptor material, and can be used in a broad variety of formats (see Hodgson, *Bio/Technology*, **1992**, *10*, 973-980; each of which is incorporated herein by reference in its entirety).

A variety of heterologous systems is available for functional expression of recombinant receptors that are well known to those skilled in the art. Such systems include bacteria (Strosberg, *et al.*, *Trends in Pharmacological Sciences*, **1992**, *13*, 95-98), yeast (Pausch, *Trends in Biotechnology*, **1997**, *15*, 487-494), several kinds of insect cells (Vanden Broeck, *Int. Rev. Cytology*, **1996**, *164*, 189-268), amphibian cells (Jayawickreme *et al.*, *Current Opinion in Biotechnology*, **1997**, *8*, 629-634) and several mammalian cell lines (CHO, HEK-293, COS, etc.; see Gerhardt, *et al.*, Eur. *J. Pharmacology*, **1997**, *334*, 1-23). These examples do not preclude the use of other possible cell expression systems, including cell lines obtained from nematodes (PCT application WO 98/37177).

In preferred embodiments of the invention, methods of screening for compounds that modulate nGPCR-x activity comprise contacting test compounds with nGPCR-x and assaying for the presence of a complex between the compound and nGPCR-x. In such assays, the ligand is typically labeled. After suitable incubation, free ligand is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular compound to bind to nGPCR-x.

It is well known that activation of heterologous receptors expressed in recombinant systems results in a variety of biological responses, which are mediated by G proteins expressed



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in the host cells. Occupation of a GPCR by an agonist results in exchange of bound GDP for GTP at a binding site on the $G_\alpha$ subunit; one can use a radioactive, non-hydrolyzable derivative of GTP, GTP$\gamma$[$^{35}$S], to measure binding of an agonist to the receptor (Sim *et al.*, Neuroreport, **1996**, *7*, 729-733). One can also use this binding to measure the ability of antagonists to bind to the receptor by decreasing binding of GTP$\gamma$[$^{35}$S] in the presence of a known agonist. One could therefore construct a HTS based on GTP$\gamma$[$^{35}$S] binding, though this is not the preferred method.

The G proteins required for functional expression of heterologous GPCRs can be native constituents of the host cell or can be introduced through well-known recombinant technology. The G proteins can be intact or chimeric. Often, a nearly universally competent G protein (e.g., $G_{\alpha 16}$) is used to couple any given receptor to a detectable response pathway. G protein activation results in the stimulation or inhibition of other native proteins, events that can be linked to a measurable response.

Examples of such biological responses include, but are not limited to, the following: the ability to survive in the absence of a limiting nutrient in specifically engineered yeast cells (Pausch, *Trends in Biotechnology*, **1997**, *15*, 487-494); changes in intracellular $Ca^{2+}$ concentration as measured by fluorescent dyes (Murphy, *et al.*, *Cur. Opinion Drug Disc. Dev.*, **1998**, *1*, 192-199). Fluorescence changes can also be used to monitor ligand-induced changes in membrane potential or intracellular pH; an automated system suitable for HTS has been described for these purposes (Schroeder, *et al.*, *J. Biomolecular Screening*, **1996**, *1*, 75-80). Melanophores prepared from *Xenopus laevis* show a ligand-dependent change in pigment organization in response to heterologous GPCR activation; this response is adaptable to HTS formats (Jayawickreme *et al.*, *Cur. Opinion Biotechnology*, **1997**, *8*, 629-634). Assays are also available for the measurement of common second messengers, including cAMP, phosphoinositides and arachidonic acid, but these are not generally preferred for HTS.

Preferred methods of HTS employing these receptors include permanently transfected CHO cells, in which agonists and antagonists can be identified by the ability to specifically alter the binding of GTP$\gamma$[$^{35}$S] in membranes prepared from these cells. In another embodiment of the invention, permanently transfected CHO cells could be used for the preparation of membranes which contain significant amounts of the recombinant receptor proteins; these membrane preparations would then be used in receptor binding assays, employing the radiolabeled ligand specific for the particular receptor. Alternatively, a functional assay, such as fluorescent monitoring of ligand-induced changes in internal $Ca^{2+}$ concentration or membrane potential in permanently transfected CHO cells containing each of these receptors individually or in combination would be preferred for HTS. Equally preferred would be an alternative type of mammalian cell, such as HEK-293 or COS cells, in similar formats. More preferred would



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be permanently transfected insect cell lines, such as *Drosophila* S2 cells. Even more preferred would be recombinant yeast cells expressing the *Drosophila melanogaster* receptors in HTS formats well known to those skilled in the art (*e.g.*, Pausch, *Trends in Biotechnology*, **1997**, *15*, 487-494).

The invention contemplates a multitude of assays to screen and identify inhibitors of ligand binding to nGPCR-x receptors. In one example, the nGPCR-x receptor is immobilized and interaction with a binding partner is assessed in the presence and absence of a candidate modulator such as an inhibitor compound. In another example, interaction between the nGPCR-x receptor and its binding partner is assessed in a solution assay, both in the presence and absence of a candidate inhibitor compound. In either assay, an inhibitor is identified as a compound that decreases binding between the nGPCR-x receptor and its binding partner. Following the identification of compounds which inhibit ligand binding to nGPCR-x receptors, such compounds may be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity. Another contemplated assay involves a variation of the dihybrid assay wherein an inhibitor of protein/protein interactions is identified by detection of a positive signal in a transformed or transfected host cell, as described in PCT publication number WO 95/20652, published August 3, 1995.

Candidate modulators contemplated by the invention include compounds selected from libraries of either potential activators or potential inhibitors. There are a number of different libraries used for the identification of small molecule modulators, including: (1) chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of random peptides, oligonucleotides or organic molecules. Chemical libraries consist of random chemical structures, some of which are analogs of known compounds or analogs of compounds that have been identified as "hits" or "leads" in other drug discovery screens, some of which are derived from natural products, and some of which arise from non-directed synthetic organic chemistry. Natural product libraries are collections of microorganisms, animals, plants, or marine organisms which are used to create mixtures for screening by: (1) fermentation and extraction of broths from soil, plant or marine microorganisms or (2) extraction of plants or marine organisms. Natural product libraries include polyketides, non-ribosomal peptides, and variants (non-naturally occurring) thereof. For a review, see Science 282:63-68 (1998). Combinatorial libraries are composed of large numbers of peptides, oligonucleotides, or organic compounds as a mixture. These libraries are relatively easy to prepare by traditional automated synthesis methods, PCR, cloning, or proprietary synthetic methods. Of particular interest are non-peptide combinatorial libraries. Still other libraries of interest include peptide, protein, peptidomimetic, multiparallel synthetic collection, recombinatorial, and polypeptide libraries. For a review of



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combinatorial chemistry and libraries created therefrom, see Myers, Curr. Opin. Biotechnol. 8:701-707 (1997). Identification of modulators through use of the various libraries described herein permits modification of the candidate "hit" (or "lead") to optimize the capacity of the "hit" to modulate activity.

Still other candidate inhibitors contemplated by the invention can be designed and include soluble forms of binding partners, as well as such binding partners as chimeric, or fusion, proteins. A "binding partner" as used herein broadly encompasses non-peptide modulators, as well as such peptide modulators as neuropeptides other than natural ligands, antibodies, antibody fragments, and modified compounds comprising antibody domains that are immunospecific for the expression product of the identified nGPCR-x gene.

The polypeptides of the invention are employed as a research tool for identification, characterization and purification of interacting, regulatory proteins. Appropriate labels are incorporated into the polypeptides of the invention by various methods known in the art and the polypeptides are used to capture interacting molecules. For example, molecules are incubated with the labeled polypeptides, washed to remove unbound polypeptides, and the polypeptide complex is quantified. Data obtained using different concentrations of polypeptide are used to calculate values for the number, affinity, and association of polypeptide with the protein complex.

Labeled polypeptides are also useful as reagents for the purification of molecules with which the polypeptide interacts including, but not limited to, inhibitors. In one embodiment of affinity purification, a polypeptide is covalently coupled to a chromatography column. Cells and their membranes are extracted, and various cellular subcomponents are passed over the column. Molecules bind to the column by virtue of their affinity to the polypeptide. The polypeptide-complex is recovered from the column, dissociated and the recovered molecule is subjected to protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotides for cloning the corresponding gene from an appropriate cDNA library.

Alternatively, compounds may be identified which exhibit similar properties to the ligand for the nGPCR-x of the invention, but which are smaller and exhibit a longer half time than the endogenous ligand in a human or animal body. When an organic compound is designed, a molecule according to the invention is used as a "lead" compound. The design of mimetics to known pharmaceutically active compounds is a well-known approach in the development of pharmaceuticals based on such "lead" compounds. Mimetic design, synthesis and testing are generally used to avoid randomly screening a large number of molecules for a target property. Furthermore, structural data deriving from the analysis of the deduced amino



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acid sequences encoded by the DNAs of the present invention are useful to design new drugs, more specific and therefore with a higher pharmacological potency.

Comparison of the protein sequence of the present invention with the sequences present in all the available databases showed a significant homology with the transmembrane portion of G protein coupled receptors. Accordingly, computer modeling can be used to develop a putative tertiary structure of the proteins of the invention based on the available information of the transmembrane domain of other proteins. Thus, novel ligands based on the predicted structure of nGPCR-x can be designed.

In a particular embodiment, the novel molecules identified by the screening methods according to the invention are low molecular weight organic molecules, in which case a composition or pharmaceutical composition can be prepared thereof for oral intake, such as in tablets. The compositions, or pharmaceutical compositions, comprising the nucleic acid molecules, vectors, polypeptides, antibodies and compounds identified by the screening methods described herein, can be prepared for any route of administration including, but not limited to, oral, intravenous, cutaneous, subcutaneous, nasal, intramuscular or intraperitoneal. The nature of the carrier or other ingredients will depend on the specific route of administration and particular embodiment of the invention to be administered. Examples of techniques and protocols that are useful in this context are, *inter alia*, found in Remington's Pharmaceutical Sciences, 16th edition, Osol, A (ed.), **1980**, which is incorporated herein by reference in its entirety.

The dosage of these low molecular weight compounds will depend on the disease state or condition to be treated and other clinical factors such as weight and condition of the human or animal and the route of administration of the compound. For treating human or animals, between approximately 0.5 mg/kg of body weight to 500 mg/kg of body weight of the compound can be administered. Therapy is typically administered at lower dosages and is continued until the desired therapeutic outcome is observed.

The present compounds and methods, including nucleic acid molecules, polypeptides, antibodies, compounds identified by the screening methods described herein, have a variety of pharmaceutical applications and may be used, for example, to treat or prevent unregulated cellular growth, such as cancer cell and tumor growth. In a particular embodiment, the present molecules are used in gene therapy. For a review of gene therapy procedures, see *e.g.* Anderson, *Science*, **1992**, *256*, 808-813, which is incorporated herein by reference in its entirety.

The present invention also encompasses a method of agonizing (stimulating) or antagonizing a nGPCR-x natural binding partner associated activity in a mammal comprising administering to said mammal an agonist or antagonist to one of the above disclosed



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polypeptides in an amount sufficient to effect said agonism or antagonism. One embodiment of the present invention, then, is a method of treating diseases in a mammal with an agonist or antagonist of the protein of the present invention comprises administering the agonist or antagonist to a mammal in an amount sufficient to agonize or antagonize nGPCR-x-associated functions.

In an effort to discover novel treatments for diseases, biomedical researchers and chemists have designed, synthesized, and tested molecules that modulate the function of G protein coupled receptors. Some small organic molecules form a class of compounds that modulate the function of G protein coupled receptors.

Exemplary diseases and conditions amenable to treatment based on the present invention include, but are not limited to, thyroid disorders (*e.g.* thyreotoxicosis, myxoedema); renal failure; inflammatory conditions (*e.g.*, Chron's disease); diseases related to cell differentiation and homeostasis; rheumatoid arthritis; autoimmune disorders; movement disorders; CNS disorders (*e.g.*, pain including migraine; stroke; psychotic and neurological disorders, including anxiety, mental disorder, manic depression, anxiety, generalized anxiety disorder, post-traumatic-stress disorder, depression, bipolar disorder, delirium, dementia, severe mental retardation; dyskinesias, such as Huntington's disease or Tourette's Syndrome; attention disorders including ADD and ADHD, and degenerative disorders such as Parkinson's, Alzheimer's; movement disorders, including ataxias, supranuclear palsy, *etc.*); infections, such as viral infections caused by HIV-1 or HIV-2; metabolic and cardiovascular diseases and disorders (*e.g.*, type 2 diabetes, impaired glucose tolerance, dyslipidemia, obesity, anorexia, hypotension, hypertension, thrombosis, myocardial infarction, cardiomyopathies, atherosclerosis, *etc.*); proliferative diseases and cancers (*e.g.*, different cancers such as breast, colon, lung, *etc.*, and hyperproliferative disorders such as psoriasis, prostate hyperplasia, *etc.*); hormonal disorders (*e.g.*, male/female hormonal replacement, polycystic ovarian syndrome, alopecia, *etc.*); sexual dysfunction, among others.

Methods of determining the dosages of compounds to be administered to a patient and modes of administering compounds to an organism are disclosed in U.S. Application Serial No. 08/702,282, filed August 23, 1996 and International patent publication number WO 96/22976, published August 1 1996, both of which are incorporated herein by reference in their entirety, including any drawings, figures or tables. Those skilled in the art will appreciate that such descriptions are applicable to the present invention and can be easily adapted to it.

The proper dosage depends on various factors such as the type of disease being treated, the particular composition being used and the size and physiological condition of the patient. Therapeutically effective doses for the compounds described herein can be estimated initially



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from cell culture and animal models. For example, a dose can be formulated in animal models to achieve a circulating concentration range that initially takes into account the $IC_{50}$ as determined in cell culture assays. The animal model data can be used to more accurately determine useful doses in humans.

Plasma half-life and biodistribution of the drug and metabolites in the plasma, tumors and major organs can also be determined to facilitate the selection of drugs most appropriate to inhibit a disorder. Such measurements can be carried out. For example, HPLC analysis can be performed on the plasma of animals treated with the drug and the location of radiolabeled compounds can be determined using detection methods such as X-ray, CAT scan and MRI. Compounds that show potent inhibitory activity in the screening assays, but have poor pharmacokinetic characteristics, can be optimized by altering the chemical structure and retesting. In this regard, compounds displaying good pharmacokinetic characteristics can be used as a model.

Toxicity studies can also be carried out by measuring the blood cell composition. For example, toxicity studies can be carried out in a suitable animal model as follows: 1) the compound is administered to mice (an untreated control mouse should also be used); 2) blood samples are periodically obtained via the tail vein from one mouse in each treatment group; and 3) the samples are analyzed for red and white blood cell counts, blood cell composition and the percent of lymphocytes versus polymorphonuclear cells. A comparison of results for each dosing regime with the controls indicates if toxicity is present.

At the termination of each toxicity study, further studies can be carried out by sacrificing the animals (preferably, in accordance with the American Veterinary Medical Association guidelines Report of the American Veterinary Medical Assoc. Panel on Euthanasia, Journal of American Veterinary Medical Assoc., 202:229-249, 1993). Representative animals from each treatment group can then be examined by gross necropsy for immediate evidence of metastasis, unusual illness or toxicity. Gross abnormalities in tissue are noted and tissues are examined histologically. Compounds causing a reduction in body weight or blood components are less preferred, as are compounds having an adverse effect on major organs. In general, the greater the adverse effect the less preferred the compound.

For the treatment of many diseases, the expected daily dose of a hydrophobic pharmaceutical agent is between 1 to 500 mg/day, preferably 1 to 250 mg/day, and most preferably 1 to 50 mg/day. Drugs can be delivered less frequently provided plasma levels of the active moiety are sufficient to maintain therapeutic effectiveness. Plasma levels should reflect the potency of the drug. Generally, the more potent the compound the lower the plasma levels necessary to achieve efficacy.



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As discussed above, it is well known that GPCRs are expressed in many different tissues and regions, including in the brain. nGPCR-x mRNA transcripts may found in many other tissues, including, but not limited to peripheral blood lymphocytes, pancreas, ovary, uterus, testis, salivary gland, kidney, adrenal gland, liver, bone marrow, prostate, fetal liver, colon, muscle, and fetal brain, and may be found in many other tissues. Within the brain, nGPCR-x mRNA transcripts may be found in many tissues, including, but not limited to, frontal lobe, hypothalamus, pons, cerebellum, caudate nucleus, and medulla.

Sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110 will, as detailed above, enable screening the endogenous neurotransmitters/hormones/ligands which activate, agonize, or antagonize nGPCR-x and for compounds with potential utility in treating disorders including, but not limited to, thyroid disorders (*e.g.* thyreotoxicosis, myxoedema); renal failure; inflammatory conditions (*e.g.*, Chron's disease); diseases related to cell differentiation and homeostasis; rheumatoid arthritis; autoimmune disorders; movement disorders; CNS disorders (*e.g.*, pain including schizophrenia, migraine; stroke; psychotic and neurological disorders, including anxiety, mental disorder, manic depression, anxiety, generalized anxiety disorder, post-traumatic-stress disorder, depression, bipolar disorder, delirium, dementia, severe mental retardation; dyskinesias, such as Huntington's disease or Tourette's Syndrome; attention disorders including ADD and ADHD, and degenerative disorders such as Parkinson's, Alzheimer's; movement disorders, including ataxias, supranuclear palsy, *etc.*); infections, such as viral infections caused by HIV-1 or HIV-2; metabolic and cardiovascular diseases and disorders (*e.g.*, type 2 diabetes, impaired glucose tolerance, dyslipidemia, obesity, anorexia, hypotension, hypertension, thrombosis, myocardial infarction, cardiomyopathies, atherosclerosis, *etc.*); proliferative diseases and cancers (*e.g.*, different cancers such as breast, colon, lung, *etc.*, and hyperproliferative disorders such as psoriasis, prostate hyperplasia, *etc.*); hormonal disorders (*e.g.*, male/female hormonal replacement, polycystic ovarian syndrome, alopecia, *etc.*); sexual dysfunction, among others.

For example, nGPCR-x may be useful in the treatment of respiratory ailments such as asthma, where T cells are implicated by the disease. Contraction of airway smooth muscle is stimulated by thrombin. Cicala *et al* (1999) Br J Pharmacol 126:478-484. Additionally, in bronchiolitis obliterans, it has been noted that activation of thrombin receptors may be deleterious. Hauck *et al.* (1999) Am J Physiol 277:L22-L29. Furthermore, mast cells have also been shown to have thrombin receptors. Cirino *et al* (1996) J Exp Med 183:821-827. nGPCR-x may also be useful in remodeling of airway structure s in chronic pulmonary inflammation via stimulation of fibroblast procollagen synthesis. See, e.g., Chambers *et al.* (1998) Biochem J 333:121-127; Trejo *et al.* (1996) J Biol Chem 271:21536-21541.



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In another example, increased release of sCD40L and expression of CD40L by T cells after activation of thrombin receptors suggests that nGPCR-x may be useful in the treatment of unstable angina due to the role of T cells and inflammation. See Aukrust *et al.* (1999) Circulation 100:614-620.

A further example is the treatment of inflammatory diseases, such as psoriasis, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, and thyroiditis. Due to the tissue expression profile of nGPCR-x, inhibition of thrombin receptors may be beneficial for these diseases. See, *e.g.*, Morris *et al.* (1996) Ann Rheum Dis 55:841-843. In addition to T cells, NK cells and monocytes are also critical cell types which contribute to the pathogenesis of these diseases. See, e.g., Naldini & Carney (1996) Cell Immunol 172:35-42; Hoffman & Cooper (1995) Blood Cells Mol Dis 21:156-167; Colotta *et al.* (1994) Am J Pathol 144:975-985.

Expression of nGPCR-x in bone marrow and spleen may suggest that it may play a role in the proliferation of hematopoietic progenitor cells. See DiCuccio *et al.* (1996) Exp Hematol 24:914-918.

As another example, nGPCR-x may be useful in the treatment of acute and/or traumatic brain injury. Astrocytes have been demonstrated to express thrombin receptors. Activation of thrombin receptors may be involved in astrogliosis following brain injury. Therefore, inhibition of receptor activity may be beneficial for limiting neuroinflammation. Scar formation mediated by astrocytes may also be limited by inhibiting thrombin receptors. See, *e.g*, Pindon *et al.* (1998) Eur J Biochem 255:766-774; Ubl & Reiser. (1997) Glia 21:361-369; Grabham & Cunningham (1995) J Neurochem 64:583-591.

nGPCR-x receptor activation may mediate neuronal and astrocyte apoptosis and prevention of neurite outgrowth. Inhibition would be beneficial in both chronic and acute brain injury. See, *e.g.*, Donovan *et al.* (1997) J Neurosci 17:5316-5326; Turgeon *et al* (1998) J Neurosci 18:6882-6891; Smith-Swintosky *et al.* (1997) J Neurochem 69:1890-1896; Gill *et al.* (1998) Brain Res 797:321-327; Suidan *et al.* (1996) Semin Thromb Hemost 22:125-133.

The attached Sequence Listing contains the sequences of the polynucleotides and polypeptides of the invention and is incorporated herein by reference in its entirety.

**Methods of Screening Human Subjects**

Thus in yet another embodiment, the invention provides genetic screening procedures that entail analyzing a person's genome -- in particular their alleles for the nGPCR-x of the invention -- to determine whether the individual possesses a genetic characteristic found in other individuals that are considered to be afflicted with, or at risk for, developing a mental disorder or disease of the brain that is suspected of having a hereditary component. For example, in one embodiment, the invention provides a method for determining a potential for developing a



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disorder affecting the brain in a human subject comprising the steps of analyzing the coding sequence of one or more nGPCR-x genes from the human subject; and determining development potential for the disorder in said human subject from the analyzing step.

More particularly, the invention provides a method of screening a human subject to diagnose a disorder affecting the brain or genetic predisposition therefor, comprising the steps of: (a) assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering the amino acid sequence, expression, or biological activity of at least one seven transmembrane receptor that is expressed in the brain, wherein the seven transmembrane receptor comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110, or an allelic variant thereof, and wherein the nucleic acid corresponds to the gene encoding the seven transmembrane receptor; and (b) diagnosing the disorder or predisposition from the presence or absence of said mutation, wherein the presence of a mutation altering the amino acid sequence, expression, or biological activity of allele in the nucleic acid correlates with an increased risk of developing the disorder.

By "human subject" is meant any human being, human embryo, or human fetus. It will be apparent that methods of the present invention will be of particular interest to individuals that have themselves been diagnosed with a disorder affecting the brain or have relatives that have been diagnosed with a disorder affecting the brain.

By "screening for an increased risk" is meant determination of whether a genetic variation exists in the human subject that correlates with a greater likelihood of developing a disorder affecting the brain than exists for the human population as a whole, or for a relevant racial or ethnic human sub-population to which the individual belongs. Both positive and negative determinations (i.e., determinations that a genetic predisposition marker is present or is absent) are intended to fall within the scope of screening methods of the invention. In preferred embodiments, the presence of a mutation altering the sequence or expression of at least one nGPCR-x seven transmembrane receptor allele in the nucleic acid is correlated with an increased risk of developing mental disorder, whereas the absence of such a mutation is reported as a negative determination.

The "assaying" step of the invention may involve any techniques available for analyzing nucleic acid to determine its characteristics, including but not limited to well-known techniques such as single-strand conformation polymorphism analysis (SSCP) [Orita *et al., Proc Natl. Acad. Sci. USA, 86*: 2766-2770 (1989)]; heteroduplex analysis [White *et al., Genomics, 12*: 301-306 (1992)]; denaturing gradient gel electrophoresis analysis [Fischer *et al., Proc. Natl. Acad. Sci. USA, 80*: 1579-1583 (1983); and Riesner *et al., Electrophoresis, 10*: 377-389 (1989)]; DNA sequencing; RNase cleavage [Myers *et al., Science, 230*: 1242-1246 (1985)]; chemical cleavage



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of mismatch techniques [Rowley *et al., Genomics, 30*: 574-582 (1995); and Roberts *et al., Nucl. Acids Res., 25*: 3377-3378 (1997)]; restriction fragment length polymorphism analysis; single nucleotide primer extension analysis [Shumaker *et al., Hum. Mutat.*, *7*: 346-354 (1996); and Pastinen *et al., Genome Res.*, *7*: 606-614 (1997)]; 5' nuclease assays [Pease *et al., Proc. Natl. Acad. Sci. USA, 91*:5022-5026 (1994)]; DNA Microchip analysis [Ramsay, G., *Nature Biotechnology, 16*: 40-48 (1999); and Chee *et al.*, U.S. Patent No. 5,837,832]; and ligase chain reaction [Whiteley *et al.*, U.S. Patent No. 5,521,065]. [See generally, Schafer and Hawkins, *Nature Biotechnology, 16*: 33-39 (1998).] All of the foregoing documents are hereby incorporated by reference in their entirety.

Thus, in one preferred embodiment involving screening nGPCR-x sequences, for example, the assaying step comprises at least one procedure selected from the group consisting of: (a) determining a nucleotide sequence of at least one codon of at least one nGPCR-x allele of the human subject; (b) performing a hybridization assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences; (c) performing a polynucleotide migration assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences; and (d) performing a restriction endonuclease digestion to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences.

In a highly preferred embodiment, the assaying involves sequencing of nucleic acid to determine nucleotide sequence thereof, using any available sequencing technique. [See, *e.g.*, Sanger *et al., Proc. Natl. Acad. Sci. (USA), 74*: 5463-5467 (1977) (dideoxy chain termination method); Mirzabekov, *TIBTECH, 12*: 27-32 (1994) (sequencing by hybridization); Drmanac *et al., Nature Biotechnology, 16*: 54-58 (1998); U.S. Patent No. 5,202,231; and *Science, 260*: 1649-1652 (1993) (sequencing by hybridization); Kieleczawa *et al., Science, 258*: 1787-1791 (1992) (sequencing by primer walking); (Douglas *et al., Biotechniques, 14*: 824-828 (1993) (Direct sequencing of PCR products); and Akane *et al., Biotechniques 16*: 238-241 (1994); Maxam and Gilbert, *Meth. Enzymol., 65*: 499-560 (1977) (chemical termination sequencing), all incorporated herein by reference.] The analysis may entail sequencing of the entire nGPCR gene genomic DNA sequence, or portions thereof; or sequencing of the entire seven transmembrane receptor coding sequence or portions thereof. In some circumstances, the analysis may involve a determination of whether an individual possesses a particular allelic variant, in which case sequencing of only a small portion of nucleic acid -- enough to determine the sequence of a particular codon characterizing the allelic variant -- is sufficient. This approach is appropriate, for example, when assaying to determine whether one family member inherited the same allelic



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variant that has been previously characterized for another family member, or, more generally, whether a person's genome contains an allelic variant that has been previously characterized and correlated with a mental disorder having a heritable component.

In another highly preferred embodiment, the assaying step comprises performing a hybridization assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences. In a preferred embodiment, the hybridization involves a determination of whether nucleic acid derived from the human subject will hybridize with one or more oligonucleotides, wherein the oligonucleotides have nucleotide sequences that correspond identically to a portion of the nGPCR-x gene sequence taught herein, or that correspond identically except for one mismatch. The hybridization conditions are selected to differentiate between perfect sequence complementarity and imperfect matches differing by one or more bases. Such hybridization experiments thereby can provide single nucleotide polymorphism sequence information about the nucleic acid from the human subject, by virtue of knowing the sequences of the oligonucleotides used in the experiments.

Several of the techniques outlined above involve an analysis wherein one performs a polynucleotide migration assay, *e.g.*, on a polyacrylamide electrophoresis gel (or in a capillary electrophoresis system), under denaturing or non-denaturing conditions. Nucleic acid derived from the human subject is subjected to gel electrophoresis, usually adjacent to (or co-loaded with) one or more reference nucleic acids, such as reference GPCR-x encoding sequences having a coding sequence identical to all or a portion of SEQ ID NOS: 1 to 110 (or identical except for one known polymorphism). The nucleic acid from the human subject and the reference sequence(s) are subjected to similar chemical or enzymatic treatments and then electrophoresed under conditions whereby the polynucleotides will show a differential migration pattern, unless they contain identical sequences. [See generally Ausubel *et al.* (eds.), *Current Protocols in Molecular Biology*, New York: John Wiley & Sons, Inc. (1987-1999); and Sambrook *et al.*, (eds.), Molecular Cloning, *A Laboratory Manual*, Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press (1989), both incorporated herein by reference in their entirety.]

In the context of assaying, the term "nucleic acid of a human subject" is intended to include nucleic acid obtained directly from the human subject (*e.g.*, DNA or RNA obtained from a biological sample such as a blood, tissue, or other cell or fluid sample); and also nucleic acid derived from nucleic acid obtained directly from the human subject. By way of non-limiting examples, well known procedures exist for creating cDNA that is complementary to RNA derived from a biological sample from a human subject, and for amplifying (*e.g.*, via



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polymerase chain reaction (PCR)) DNA or RNA derived from a biological sample obtained from a human subject. Any such derived polynucleotide which retains relevant nucleotide sequence information of the human subject's own DNA/RNA is intended to fall within the definition of "nucleic acid of a human subject" for the purposes of the present invention.

In the context of assaying, the term "mutation" includes addition, deletion, and/or substitution of one or more nucleotides in the GPCR gene sequence (*e.g.*, as compared to the seven transmembrane receptor-encoding sequences set forth of SEQ ID NO:1 to SEQ ID NO:110, and other polymorphisms that occur in introns (where introns exist) and that are identifiable via sequencing, restriction fragment length polymorphism, or other techniques. The various activity examples provided herein permit determination of whether a mutation modulates activity of the relevant receptor in the presence or absence of various test substances.

In a related embodiment, the invention provides methods of screening a person's genotype with respect to the nGPCR-x of the invention, and correlating such genotypes with diagnoses for disease or with predisposition for disease (for genetic counseling). For example, the invention provides a method of screening for an nGPCR-x hereditary mental disorder genotype in a human patient, comprising the steps of: (a) providing a biological sample comprising nucleic acid from the patient, the nucleic acid including sequences corresponding to said patient's nGPCR-x alleles; (b) analyzing the nucleic acid for the presence of a mutation or mutations; (c) determining a nGPCR-x genotype from the analyzing step; and (d) correlating the presence of a mutation in an nGPCR-x allele with a hereditary mental disorder genotype. In a preferred embodiment, the biological sample is a cell sample containing human cells that contain genomic DNA of the human subject. The analyzing can be performed analogously to the assaying described in preceding paragraphs. For example, the analyzing comprises sequencing a portion of the nucleic acid (e.g., DNA or RNA), the portion comprising at least one codon of the nGPCR-x alleles.

Although more time consuming and expensive than methods involving nucleic acid analysis, the invention also may be practiced by assaying one or more proteins of a human subject to determine the presence or absence of an amino acid sequence variation in GPCR protein from the human subject. Such protein analyses may be performed, *e.g.*, by fragmenting GPCR protein via chemical or enzymatic methods and sequencing the resultant peptides; or by Western analyses using an antibody having specificity for a particular allelic variant of the GPCR.

The invention also provides materials that are useful for performing methods of the invention. For example, the present invention provides oligonucleotides useful as probes in the many analyzing techniques described above. In general, such oligonucleotide probes comprise



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6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 nucleotides that have a sequence that is identical, or exactly complementary, to a portion of a human GPCR gene sequence taught herein (or allelic variant thereof), or that is identical or exactly complementary except for one nucleotide substitution. In a preferred embodiment, the oligonucleotides have a sequence that corresponds in the foregoing manner to a human GPCR coding sequence taught herein, and in particular, the coding sequences set forth in SEQ ID NO:1 to SEQ ID NO:110. In one variation, an oligonucleotide probe of the invention is purified and isolated. In another variation, the oligonucleotide probe is labeled, *e.g.*, with a radioisotope, chromophore, or fluorophore. In yet another variation, the probe is covalently attached to a solid support. [See generally Ausubel *et al.* and Sambrook *et al.*, *supra.*]

In a related embodiment, the invention provides kits comprising reagents that are useful for practicing methods of the invention. For example, the invention provides a kit for screening a human subject to diagnose a mental disorder or a genetic predisposition therefor, comprising, in association: (a) an oligonucleotide useful as a probe for identifying polymorphisms in a human nGPCR-x seven transmembrane receptor gene, the oligonucleotide comprising 6-50 nucleotides that have a sequence that is identical or exactly complementary to a portion of a human nGPCR-x gene sequence or nGPCR-x coding sequence, except for one sequence difference selected from the group consisting of a nucleotide addition, a nucleotide deletion, or nucleotide substitution; and (b) a media packaged with the oligonucleotide containing information identifying polymorphisms identifiable with the probe that correlate with mental disorder or a genetic predisposition therefor. Exemplary information-containing media include printed paper package inserts or packaging labels; and magnetic and optical storage media that are readable by computers or machines used by practitioners who perform genetic screening and counseling services. The practitioner uses the information provided in the media to correlate the results of the analysis with the oligonucleotide with a diagnosis. In a preferred variation, the oligonucleotide is labeled.

In still another embodiment, the invention provides methods of identifying those allelic variants of GPCRs of the invention that correlate with mental disorders. For example, the invention provides a method of identifying a seven transmembrane allelic variant that correlates with a mental disorder, comprising steps of: (a) providing a biological sample comprising nucleic acid from a human patient diagnosed with a mental disorder, or from the patient's genetic progenitors or progeny; (b) analyzing the nucleic acid for the presence of a mutation or mutations in at least one seven transmembrane receptor that is expressed in the brain, wherein the at least one seven transmembrane receptor comprises an amino acid sequence selected from



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the group consisting of SEQ ID NO:1 to SEQ ID NO:110 or an allelic variant thereof, and wherein the nucleic acid includes sequence corresponding to the gene or genes encoding the at least one seven transmembrane receptor; (c) determining a genotype for the patient for the at least one seven transmembrane receptor from said analyzing step; and (d) identifying an allelic variant that correlates with the mental disorder from the determining step. To expedite this process, it may be desirable to perform linkage studies in the patients (and possibly their families) to correlate chromosomal markers with disease states. The chromosomal localization data provided herein facilitates identifying an involved nGPCR with a chromosomal marker.

The foregoing method can be performed to correlate the nGPCR-x of the invention to a number of disorders having hereditary components that are causative or that predispose persons to the disorder. For example, in one preferred variation, the disorder is a mental disorder.

Also contemplated as part of the invention are polynucleotides that comprise the allelic variant sequences identified by such methods, and polypeptides encoded by the allelic variant sequences, and oligonucleotide and oligopeptide fragments thereof that embody the mutations that have been identified. Such materials are useful in *in vitro* cell-free and cell-based assays for identifying lead compounds and therapeutics for treatment of the disorders. For example, the variants are used in activity assays, binding assays, and assays to screen for activity modulators described herein. In one preferred embodiment, the invention provides a purified and isolated polynucleotide comprising a nucleotide sequence encoding a nGPCR-x receptor allelic variant identified according to the methods described above; and an oligonucleotide that comprises the sequences that differentiate the allelic variant from the nGPCR-x sequences set forth in SEQ ID NO:1 to SEQ ID NO:110. The invention also provides a vector comprising the polynucleotide (preferably an expression vector); and a host cell transformed or transfected with the polynucleotide or vector. The invention also provides an isolated cell line that is expressing the allelic variant nGPCR-x polypeptide; purified cell membranes from such cells; purified polypeptide; and synthetic peptides that embody the allelic variation amino acid sequence. In one particular embodiment, the invention provides a purified polynucleotide comprising a nucleotide sequence encoding a nGPCR-x seven transmembrane receptor protein of a human that is affected with a mental disorder; wherein said polynucleotide hybridizes to the complement of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110 under the following hybridization conditions: (a) hybridization for 16 hours at 42°C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% dextran sulfate and (b) washing 2 times for 30 minutes at 60°C in a wash solution comprising 0.1x SSC and 1% SDS; and wherein the polynucleotide encodes a nGPCR-x amino acid sequence that differs from



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a sequence selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220, by at least one residue.

An exemplary assay for using the allelic variants is a method for identifying a modulator of nGPCR-x biological activity, comprising the steps of: (a) contacting a cell expressing the allelic variant in the presence and in the absence of a putative modulator compound; (b) measuring nGPCR-x biological activity in the cell; and (c) identifying a putative modulator compound in view of decreased or increased nGPCR-x biological activity in the presence versus absence of the putative modulator.

Additional features of the invention will be apparent from the following Examples. Examples 1 and 2 are actual while the remaining Examples are prophetic. Additional features and variations of the invention will be apparent to those skilled in the art from the entirety of this application, including the detailed description, and all such features are intended as aspects of the invention. Likewise, features of the invention described herein can be re-combined into additional embodiments that also are intended as aspects of the invention, irrespective of whether the combination of features is specifically mentioned above as an aspect or embodiment of the invention. Also, only such limitations which are described herein as critical to the invention should be viewed as such; variations of the invention lacking limitations which have not been described herein as critical are intended as aspects of the invention.

## EXAMPLES

### EXAMPLE 1: IDENTIFICATION OF nGPCR-X

A. Database search

The Celera database was searched using known GPCR receptors as query sequences to find patterns suggestive of novel G protein-coupled receptors. Positive hits were further analyzed with the GCG program BLAST to determine which ones were the most likely candidates to encode G protein-coupled receptors, using the standard (default) alignment produced by BLAST as a guide.

Briefly, the BLAST algorithm, which stands for Basic Local Alignment Search Tool is suitable for determining sequence similarity (Altschul *et al.*, J. Mol. Biol., 1990, 215, 403-410, which is incorporated herein by reference in its entirety). Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/). This algorithm involves first identifying high scoring sequence pair (HSPs) by identifying short words of length W in the query sequence that either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*,



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*supra*). These initial neighborhood word hits act as seeds for initiating searches to find HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Extension for the word hits in each direction are halted when: 1) the cumulative alignment score falls off by the quantity X from its maximum achieved value; 2) the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or 3) the end of either sequence is reached. The Blast algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The Blast program uses as defaults a word length (W) of 11, the BLOSUM62 scoring matrix (see Henikoff et al., Proc. Natl. Acad. Sci. USA, 1992, 89, 10915-10919, which is incorporated herein by reference in its entirety) alignments (B) of 50, expectation (E) of 10, M=5, N=4, and a comparison of both strands.

The BLAST algorithm (Karlin *et al.*, Proc. Natl. Acad. Sci. USA, 1993, 90, 5873-5787, which is incorporated herein by reference in its entirety) and Gapped BLAST perform a statistical analysis of the similarity between two sequences. One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a GPCR gene or cDNA if the smallest sum probability in comparison of the test nucleic acid to a GPCR nucleic acid is less than about 1, preferably less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

Homology searches are performed with the program BLAST version 2.08. A collection of 340 query amino acid sequences derived from GPCRs was used to search the genomic DNA sequence using TBLASTN and alignments with an E-value lower than 0.01 were collected from each BLAST search. The amino acid sequences have been edited to remove regions in the sequence that produce non-significant alignments with proteins that are not related to GPCRs.

Multiple query sequences may have a significant alignment to the same genomic region, although each alignment may not cover exactly the same DNA region. A procedure is used to determine the region of maximum common overlap between the alignments from several query sequences. This region is called the consensus DNA region. The procedure for determining this consensus involves the automatic parsing of the BLAST output files using the program MSPcrunch to produce a tabular report. From this tabular report the start and end of each alignment in the genomic DNA is extracted. This information is used by a PERL script to derive the maximum common overlap. These regions are reported in the form of a unique sequence identifier, a start and the end position in the sequence. The sequences defined by these regions were extracted from the original genomic sequence file using the program fetchdb.



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The consensus regions are assembled into a non-redundant set by using the program phrap. After assembly with phrap a set of contigs and singletons were defined as candidate DNA regions coding for nGPCRs. These sequences were then submitted for further sequence analysis.

Further sequence analysis involves the removal of sequences previously isolated and removal of sequences that are related to olfactory GPCR's.

nGPRCR-x cDNAs were sequenced directly using an ABI377 fluorescence-based sequencer (Perkin-Elmer/Applied Biosystems Division, PE/ABD, Foster City, CA) and the ABI PRISM™ Ready Dye-Deoxy Terminator kit with Taq FS™ polymerase. Each ABI cycle sequencing reaction contained about 0.5 μg of plasmid DNA. Cycle-sequencing was performed using an initial denaturation at 98°C for 1 minute, followed by 50 cycles using the following parameters: 98°C for 30 seconds, annealing at 50°C for 30 seconds, and extension at 60°C for 4 minutes. Temperature cycles and times were controlled by a Perkin-Elmer 9600 thermocycler. Extension products were purified using Centriflex™ gel filtration cartridges (Advanced Genetic Technologies Corp., Gaithersburg, MD). Each reaction product was loaded by pipette onto the column, which is then centrifuged in a swinging bucket centrifuge (Sorvall model RT6000B tabletop centrifuge) at 1500 x *g* for 4 minutes at room temperature. Column-purified samples were dried under vacuum for about 40 minutes and then dissolved in 5μl of a DNA loading solution (83% deionized formamide, 8.3mM EDTA, and 1.6 mg/ml Blue Dextran). The samples were then heated to 90°C for three minutes and loaded into the gel sample wells for sequence analysis using the ABI377 sequencer. Sequence analysis was performed by importing ABI377 files into the Sequencer program (Gene Codes, Ann Arbor, MI). Generally, sequence reads of 700 bp were obtained. Potential sequencing errors were minimized by obtaining sequence information from both DNA strands and by re-sequencing difficult areas using primers annealing at different locations until all sequencing ambiguities were removed.

The following Table 5 contains the sequences of the polynucleotides and polypeptides of the invention. The transmembrane domains within the polypeptide sequence are identified by underlining.

| **Table 5** |
|---|
| The following DNA sequence nGPCR-2031 <SEQ ID NO.1> was identified in *H. sapiens*:<br>CCAAATCCCATCTTTCTCTCCTTTGACAAACTAGGAATTGCTATTGTTCCCTTGGTAAACATAGTAGGGAT<br>ATGAAATAAGACAATTTAATCCTCTAATTTATGACAATGGGAGAGATGTTGCTGAAAACCCTGAGCTATCA<br>GTGCTTTTAATTAAAACAACATTAGTAATGGTCACTAAAGGAAAATATATTCCATTGTAAATGTCAAGATT<br>TACACTGTCTCTGACAATGACACAATAATTATGCTAAGGTGCAGAAAGTAACACCGCCTCACTAATTCTCC<br>TGCAACACAAAATATACAGTGAAAGTGACAAATGGATTAATTTACATATGGATGAACATGATCTGTTGCTC<br>TCCAAGGTCCCAAAAGATACATAAGAGAAAAATTTAGTGATGTTACTGGATGATGTCTTTTAAGACAACAC |



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AATACAATATCTGAGTATGTACCCTTACGACATAGAGAAGGGATTTCAAAATATTTTAACTTAAATAGAT
TCACTAAAAGAAATCACCTTCCAACCACTGTTCCTTGTCTCTGGTCAATTAGGGTCATAATATTGTTTTCA
TTGTATTACAAAAGGTAAGAATGTACACTGTTTAAATGAATAAATAATATAGATTACTAGATAAGCAG

The following amino acid sequence <SEQ ID NO.111> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 1:
QIPSFSPLTNELLLFPWTGYEIRQFNPLIYDNGRDVAENPELSVLLIKTTLVMVTKGKYIPLMSRFTLSLT
MTQLCGAESNTASLILLQHKIYSESDKWINLHMDEHDLLLSKVPKDTEKNLVMLLDDVFDNTIQYLSMYPY
DIEKGFSKYFNLNRFTKRNHLPTTVPCLWSIRVIILFSLYYKRECTLFKINNIDYIS

The following DNA sequence nGPCR-2032 <SEQ ID NO.2> was identified in *H. sapiens*:
ATGAATTGAAAACAGAAAATGTATGTAAATATGTATGAAAATATGTATATAAAAATATGTATTTTTAAAGT
TACTTTTAAAAGTCTTTCATATTATATATTACACACACACACACACACACACACACGATGTGAAGATCACT
TCTAACCACCCAATATAAGATTATATTTTTAAGAAATATAGTGTTCAAATATTGTTTTATCCCATATAAGA
GCAATTTATGGCTGTTTTATGGGTTTCATCAGGCTATGTCACTCTAAACCAACTTTGCTAACAAAGGGTAA
ACACAGTAGGGAATGAAATATCTTTTAACAAATAAGAAACCCAGCAACAGCATGTATGTGATAGGAAAAAT
TAAAAGTTCCTGAGTAAATAGTATACATGAATTGACTTCAATCTGAAGTGCTTTGTTATCCCTGAAAATTA
GTTAAAATTCATTGAAGATTATTAGGACCCATTTGAATGTTTCATCTACTTGGATTGGGTGTCTTTTTAGT
ATCAGAACTGAACGATACCTATTAGATTGAATATTTTACACTCATAAGAGGTTTAAAAAACTAATCAACAG
AAGTAGACTGCATGTTAACTAATCACTAAGTGACTCTTGATCAGAATTGAGCATTGCCAAGAGGCTCTCAA
ACAGAAGAGATCATGCCCTTTCTTTCTTAAGAGGACCCTGCTGCATAACTGTGTTACAGTTTCTTCAGTGA
AGGAGAACTCTAAAGAAAACCACACTATGA

The following amino acid sequence <SEQ ID NO.112> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.2:
ELKTENVCKYVKYVYKNMYFSYFKSFILYITHTHTHTHTMRSLLTTQYKIIFLRNIVFKYCFIPYKSNLWL
FYGFHQAMSLTNFANKGTQGMKYLLTNKKPSNSMYVIGKIKSSVNSIHELTSISALLSLKISNSLKIIRTH
LNVSSTWIGCLFSIRTERYLLDIFYTHKRFKKLINRSRLHVNSLSDSSELSIAKRLSNRRDHALSFLRGPC
CITVLQFLQRRTLKKTTL

The following DNA sequence nGPCR-2033 <SEQ ID NO.3> was identified in *H. sapiens*:
CTGGTTTGTGATTATAGTTGGTTGTTTTATTATTACATTTTATAATTTGTACTCATTCAGTATTACATATG
TTGCTATATCTATGTCTTTATATCTACATCAGTATCTTTTGATATACATTGAAATCAAGTTTAGCCTTCAA
AGATCAAGAAGACATCCTTTAATATCACACATTGACTATTGGTATTGACTTCTAACTTATCTCCTTGTTA
ATATGTGGCCCCCCGTGAAATGTACACATTGCTATCTCAGTAAGTTATTTTAATATGTACAGAGTCATAGT
TGACATCCTTGAAATTATTAGTGGTCTCACATTATTTATGAACTAAATTCAAACCTTAATAGTATTGATGTA
CAGACCCTTTAGAGCTGGCTCTTTTTTATCTTTCCAATCTTACTATAATATAGTTTCTATCTATCCCAAAC
AGCAGCCATTTCTGACTTCTTGCAGTTCTGTAAATCAACCAAATGGCTTTGCCGCTCTAATTATGTCTTCA
CCTACCTTCATCTGCATAGAATGCTATTTCTCATCTGACTTTGTTTCTCCGGAGAAGACCTAATTCTCTTT
GAAGGCAATGCCTTACATAAAAACTCTTCCTTCTCTCCTCAAAATTAAGAAGTCCTGACATTCATCTTTTG
GGTCCTCACTCTCAATGTGCATACTTA

The following amino acid sequence <SEQ ID NO.113> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.3:
WFVIIVGCFIITFYNLYSFSITYVAISMSLYLHQYLLIYIEIKFSLQRSRRHPLISHIDYWLLTSNLSPCY
VAPREMYTLLSQVILICTESLTSLKLLVVSHYLTKFKPYDVQTLSWLFFIFPILLYSFYLSQTAAISDFLQ
FCKSTKWLCRSNYVFTYLHLHRMLFLILCFSGEDLILFEGNALHKNSSFSPQNEVLTFIFWVLTLNVHT

The following DNA sequence nGPCR-2034 <SEQ ID NO.4> was identified in *H. sapiens*:
ACTTCCCCTCGCAGTTATACCTATGCAAAGCATGTTTATGAGGATGTTTGTGGGGACAGTATAAAAAGGAA
ATGTAAAATTTTCATTTTCTTTGCTATCTGAGACATATCCAAGAAAATAAAAGGCATTTTACAGTTTTGGC
ATAAAGAATGTAAGTGATATTACATTCTTATATCTTTAGAGAGAGGGGGATTCAATTAAGCAAACCAGCAG
AAGAATGAAAAGAGAAACGTGAGCAGTATATGCAGTAACCATTGCAGAATTGGCACAATTGTAGATTTATA
AAAGGCAGTGTGCTCTCTTACTTCCCCCCGAGTGCAAGCCTTCACCTGCCCTTGACTGACTATCCAGGACA
TTGTCAGGCACTGAGCATTGATCTATCACAGGTGTAATTTGTGATCGACTTGATGCAATGTGTTTAACTCC
AAAATCAGATTGGTTGGGAAAAAATGCTTCTCAGAACGGTATGAGGATTTCATCAACAAAGTTTATGTGTA
CCTGGAA

The following amino acid sequence <SEQ ID NO.114> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.4:
SRYTTLLMKSSYRSEKHFFPTNLILELNTLHQVDHKLHLINAQCLTMSWIVSQGQVKACTRGEVREHTAFY



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KSTIVPILQWLLHILLTFLFSFFCWFALNPPLSKDIRMYHLHSLCQNCKMPFIFLDMSQIAKKMKILHFLF
ILSPQTSSTCFAVLRGE

The following DNA sequence nGPCR-2035 <SEQ ID NO.5> was identified in *H. sapiens*:
CTATAAACTAGGTGGCTTAAAACAACAAAAATTTATTCTGTTCTAGTTCTGGAGGCTAGAAGTCTAAAGAA
AATCAAGGCGTCAGCAGAATGGAAGCCCTAGAATAGTCTAGGGAGGAATTCTTCATTTTTTCCTTGCTTCT
GGTGGCTCCCAGCAATCTTGGTATTCCTTGGTTTGTAGCTGCATCACTCCAATTTTTGCCTTCATCTTTCC
ATGAACTTATTTCCTGTGTGTGTCTCTGCATCTCCTCTCTTTTTATGGGGTGCCAGTTATTAGATTTAAGG
CCCACTCTAACCCAGTATGAGCTCATCTTAACTTGATTACATCTGCAAAGACCTTATCTCCAAATAAGGTC
ACCTTCTGAGGTTCTTGGTAGACATACATTTTGGGGGGATACTATTCAACTCATTACACCACAACCCCCCA
AACTAGAGAGATAGGCAAATACAGAGAATCACAGGTTACAGGGAGCAGAAGCCTCTAAATGCAATACCTGA
TAGAAACACTTAAACAATAATTGACACATTGCTGGAGGCTGGAGTGTGGACTAACTTGAGACATAAAAACT
CTTGAGGGCCTAGACTTGTGGGGAGGACACCCACTTTCATAAGTTTTATCTCTAGGAGCCCCACCAGGTTC
TCATGATAAAGTGCTGAGAA

The following amino acid sequence <SEQ ID NO.115> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.5:
INVANNKNLFCSSSGGKSKENQGVSRMEALESREEFFIFSLLLVAPSNLGIPWFVAASLQFLPSSFHELIS
CVCLCISSLFMGCQLLDLRPTLTQYELILTLHLQRPYLQIRSPSEVLGRHTFWGDTIQLITPQPPKLERAN
TENHRLQGAEASKCNTKHLNNNHIAGGWSVDLETKLLRATCGEDTHFHKFYLEPHQVLMIKCE

The following DNA sequence nGPCR-2036 <SEQ ID NO.6> was identified in *H. sapiens*:
GATGCATTAGTGCTGCATTAAATACTTACTCAAAAAGGAGTAGAAGTCTTGCAGAATGGGTAACAATGTAA
AAGTCCAAAAGGAAAACCTAGGAAGGGAATCAATATTTCCAAGGCCTGTATCTGCTTTCTGGTACTTACCC
ACACCTTGCCGCAATTCCCAACCAAGTTAATAGATGTGAACTGAAGAAGATTACTACATTCTACTGCATGA
TACTGTGATATATATCTAAAAATACTTTTCCACTCCTGAAAATATTCAGTCTTATACCTATATACATTTAG
AAATGACAAATAGAAAACAGTATATATTCTCAAATGCAAAACTGCAAACAGTTTGAAGAATGGCCTAAACA
AAGAATACACACACACATACATAAATATATATATATATATACACACACACACACACACACACAAGCACCCA
CACACCTGTGCCCTTAAGGCGCTCAGAGTCTATTCTGATAGTTATCCACTTACACAAAAATGTACACTAAT
AGTGATGAGAAAGTAGCAGCACAGAAGAAGGAGATGTTGCTCTGGGGTAGAAAAGAAAGTTTGCAAGTCCT
GGATGCCCAGTGACTTACGTTTTGTTCAACCACCTAGTTTAATTACCATCCATTCCACTAGGAGTTAAAGA
ATAAATATATTCAGTACAATGCCAGTTTACTATTTAT

The following amino acid sequence <SEQ ID NO.116> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.6:
KTGIVLNIFILLLVEWMVIKLGGTKRKSLGIQDLQTFFSTPEQHLLLLCCYFLITISVHFCVSGLSETLSA
LRAQVCGCLCVCVCVCIYIYIFMYVCVYSLFRPFFKLFAVLHLRIYTVFYLSFLNVYRYKTEYFQEWKSIF
RYISQYHAVECSNLLQFTSINLVGNCGKVWVSTRKQIQALEILIPFLGFPFGLLHCYPFCKTSTPFVSICS
TNA

The following DNA sequence nGPCR-2037 <SEQ ID NO.7> was identified in *H. sapiens*:
TTTTATAATTCCTAATGGTAATAATTATATCAGTTTGTAAAGTCAGCAATATTGATAAGCAGCAGTACAAG
TAAATACAATAATCACAGTTTGTTTTGCTTTGAAACTTAAATCTATTTAACACCTTCCCCTGTCTCTTGAT
CTTCATGTTCCCAGGGGATAGGGTCATTGTCCTGTACAGAAGGGACTGTGTCCCTCTCATGCCAAAACTGC
TCTACGTCAGGAAGGATGGGAATCTCTGCCTTCTCAGTTTTCCCTTTGCCAGAGGAGGGAGAGCTGGGTTT
CTCTTTTTCTGGTATGGATGCTGGGGATTCTGGAGATGGAACCTTGTCAGGAAGACCCCTCTGAGTTGCCAG
CTGGTGTTTCCTGAGACTCTGAGACAGTTGGAGGTTTTTTGGTTATCATCCATTTCCATACACCTTTCAAG
CCTTCCCTGAACTCTTCCGACATCACAAGAAAAATGAGAGGATTTGCTGAAGAGATGGAAAACATCAAGAC
TTGAGACAGGGCTATGAAACCTTGTGGTGGGGCCGGGCCTGCAGCCTTCAGATGCCATACCCACAGCCAAG
CTACCCATTCGGGGAGCCACAAGAGAGCAGAGATGATGGCAATGCTCAGCAGCATCACTGTGACTTGCTTT
GGAGCGTATCTGGTTTCTAAGATTTTGAGTCTTAGTTCCTCGTTTTTTACATTGGTCATAAGCTCTCCAGA
AATAAAAGCTGGCAAAAAAATAAT

The following amino acid sequence <SEQ ID NO.117> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.7:
YFLPAFISGELMTNVKNEELRLKILETRYAPKQVTVMLLSIAIISALLWLPEWVAWLWVWHLKAAGPAPPQ
GFIALSQVLMFSISSANPLIFLVMSEEFREGLKGVWKWMITKKPPTVSESQETPAGNSEGLPDKVPSPESP
ASIPEKEKPSSPSSGKGKTEKAEIPILPDVEQFWHERDTVPSVQDNDPIPWEHEDQETGEGVKIVSKQNKL
LLYLLVLLLINIADFTNYNYYHEL

The following DNA sequence nGPCR-2038 <SEQ ID NO.8> was identified in



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*H. sapiens*:
CTGTTGCCCTATCCTGGGGTACACTTATTTGCAGAGCCTTTGTTGCTAGGGCTGAGTCCCTGCTCTTCTTT
GTGGTCCTTCTCCAACAGAGCCAGCATGGCTGCAGATCCCCTACCACCAGCATAGAGACGAAGGAACAGGA
GAGGAGTGAAGGTCTGACCAGACCAGATTGGCCACCCCAGACCCCAGCAGGCACAGCAATGCACCAGCGTG
CAGGCAGCCCCATTCGCCGGAGTCACCATGCCCAGCCCAACAGGCTGCCTTTGTTTTTATGGTGATTTTTG
CACGCTCATCCTTACACGATGCACGAATGGGGTTGGAATGGGTCTTTGGCAGAAAGCAGTGGCATCTGTCA
TCTTTGCTTCACCACGATTCCAGCTCAGCACCAGGCCTCTGGTAGCGCATTTCCTCCTCATCACATTTGTT
CCTGTTGACTGACCAGATTATTGATCGCTCTGTTCTGCAGCACTGGGTCGGTTAAGCTTGGTTGCCTCCAG
GCCTCTGCTTTGGAGTAAATCTCCATGAGCCAAACTAAATTCCTCAGTAGTACAAAACAGATTTTAACATT
TGCAGGAGAAAAATAAAATGACACAAATAGTCACACACCCAAACCACACAGTGCAAAGAGTAAAGGTAGAT
ATTGCAGCAGCAAGTCGTTTAGACATCAC

The following amino acid sequence <SEQ ID NO.118> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.8:
LLPYPGVHLFAEPLLLGLSPCSSLWSFSNRGRMAADPLPPARRRNRRGVKVPDQIGHPRPQQAQQCTSVQA
APFAGVTMPSPTGCLCFYGDFCTLILTRCTNGVGMGLWQKAVASVIFASPRFQLSTRPLVAHFLLITFVPV
DPDYSLCSAALGGLSLVASRPLLWSKSPAKLNSSVVQNRFHLQEKNKMTQIVTHPNHTVQRVKVDIAAASR
LDI

The following DNA sequence nGPCR-2039 <SEQ ID NO.9> was identified in *H. sapiens*:
CCGAAAGTGTGCACGGGAGGCCATATGTACCAGGCACTGGTTATGTCCTGGGAAAACATTTGCATAAGGCT
CAAAATTGTCTTAGCCATTCATGAAAGCATGAATTCTGGGGCAGAGGTAATAGAGACAACAAAGTCATAAC
AATGGAAAGCCTACTTAGAAAATGAAGGACTGATTGGGCTTCAGCTTTTATTCACTCATTTATCTGCTCCC
AAACATGCATCGAGCATCTCGAGTGGAGCCCTGTGTGCATTCTGGTAAGACTGGATGGATCAAGGGATTTC
CTGCCCTTGAGAAGCTTGCAGAATCCTGGGAGAGAGATATTTCCACACATAGTTACAGTATGCCCTCCCGG
GGAACTCTTGACCTGGGGAAAAGAGCCAGGAAAGATGTGTTTGAGCTGTGCCTGCCTAGATGTCACTTCCA
GTGTGAGGAGCCAAGAGAAGGTGGCACGATGCAGGAGGCAAGTGGCAAGGATCCTCTTATTTGAGCCTAGT
GTGATGAGAAGGCAGATGTGTTAAGATGTACATTTCTTATGTCTTTTTTAGCTTTTTTTTTTCAATAAGAA
TGTAGTATTTGATTGTAGGAATAAGGCTTCAATAATCAAGTTTGCTTGTATGCTTAATGAGAGCATGTGAT
GCCT

The following amino acid sequence <SEQ ID NO.119> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.9:
ESVHGRPYVPGTGYVLGKHLHKAQNCLSHSKHEFWGRGNRDNKVITMESLLRKRTDWASAFIHSFICSQTC
IEHLEWSPVCILVRLDGSRDFLPLRSLQNPGREIFPHIVTVCPPGELLTWGKEPGKMCLSCACLDVTSSVR
SQEKVARCRRQVARILLFEPSVMRRQMCDVHFLCLFLFFFNKNVVFDCRNKASIIKFACMLNESMC

The following DNA sequence nGPCR-2040 <SEQ ID NO.10> was identified in *H. sapiens*:
AGTTCGCCACTCTCAGGGGACCTGGGTGAGTGAGACACTTACCCATTCTCTCCACTCACAGTAAACCAATC
TGTGCAGTGGCAGCAGAGTGGCTCGGGTGTGAGGTGCTGGGGATGTGACTGAGACACCTCCCACCCCCACC
ACCACTGACAGAGACACACGTGGACACAGCAGATAACCTGGCGCTTTCATAGGTGGTGGAGCCCAGCACCA
GCCCTGGAAGGAGGAGCAGCCATCCCAGACTGGGGAGGGCGTGCCCAGGTCATATGATTCAGGGACTGAT
CCCCTTCCAGGTGGAGGGGCAGGTGAGTTGGGGGTGTGGTGAGTGCAATGGTGGGGAGGCCCGAGGAGGGT
AAGGTGGCCAGAGCAAAGAGGGGCCCCAGAGGCTGCAGGTGGAATGGTGAATGTCCTGATTTCTGCTGTGC
TCAGCACACAGCGGTGTTGAGAACAGAGACAGAGCCCAAGAATAGAGGCACACGGGGAAGTAGACAACATC
GACACTGCCACAGGGGCAGGCGGCCCATCTGGTGTTGGCCCTGTG

The following amino acid sequence <SEQ ID NO.120> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.10:
TGPTPDGPPAPVAVSMLSTSPCASILGLCLCSQHRCVLSTAEIRTFTIPPAASGAPLCSGHLTLLGPPHHC
THHTPNSPAPPPGRGSVPESYDLGTPSPSLGWLLLLPGLVLGSTTYESARLSAVSTCVSVSGGGGGRCLSH
IPSTSHPSHSAATAQIGLLVERMGKCLTHPGPLRVAN

The following DNA sequence nGPCR-2041 <SEQ ID NO.11> was identified in *H. sapiens*:
TTGTGTTTTATGTTTTCCATTAAAAATATTCCTCTGTGAAGTTGAACAAAATATTCTTAAGTAATCAGTTC
TACAGTGAAACAAAGGAAGAAAACCTCTGCTGTTATAAACCAAAACTGGTGTTGGAATTGGAATGAGCTTG
GGGAAGCACAGGCACCTCTGAATTATATTAAGATATTTCAAAGTCTTTCACTTACCTGTCCACACTCATTA
CAGTCATGATGGCACTACAGGCAAATTGGTTACAAGTATCCAGGGATGTGATGATGGTGCAGAGAGGCCCC
CCAAACACCCACTCTCCCCCTCGGCCCATTGGTGAATAAGAAAAGGCATTCCAACTATGTGGACCAAATC
AGCCACAGCCAGGTTGCAGATATAGATGTCAGGGACTGTTTTTTTCCTGGATCTGAAAGAGATAGAGGAAA
CTGAGGATTGACATTGAATGTATACAGACTATTCGATATATGCTACCTCATACAAATTTTTAATTGACATA



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ATGCATTTTAAATGTTAAAGGAAAACCTATACAGATGCATAGAGGAAATGCCTAGTCTTGTGTGTATTTAA
GCATTTTGAACTATTTATTTGATAACTTACTGGGGGGGGGTTAAAAATATGTCCACAAAATATTTGATAT
TCCTTTCAGTAGGTGGAGCCTAATTCCCTCTGAGTGCTGACCTTATTAACTTGCTTCTAACATGAGAATAT
GGCAGAAGTGCAGTGTGTGACTTTG

The following amino acid sequence <SEQ ID NO.121> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.11:
KSHTALLPYSHVRSKLIRSALRGNAPPTERNIKYFVDIFLTPPPVSYQINSSKCLNTHKTRHFLYASVVFL
HLKCIMSIKNLYEVAYIESVYIQCQSSVSSISFRSRKKTVPDIYICNLAVADLVHIVGMPFLIHQWARGGE
WVFGGPLCTIITSLDTCNQFACSAIMTVMSVDRVKDFEISYNSEVPVLPQAHSNSNTSFGLQQRFSSFVSL
NLLKNILFNFTEEYFWKTNT

The following DNA sequence nGPCR-2042 <SEQ ID NO.12> was identified in *H. sapiens*:
CTGCTAATTGCCAGCCAGTGGAAGAAGAAGCAGAGGCCATTGTGGCTTGAGATGAATTCTCTGCATGGCAG
CACCAGGTAGAGGTTAAGAGGGAGCCAGCTGATTGTGTAGACAAGCACCATTGTCATCAGCATCTTCAGGG
TCTCCTTCTTCTCCCCATGCTGCCAGATATAGGTGTGGATGCTGATGTCATCAACAGCATTATGGATCCAC
AGCTTTTTGGCCACATGACCATAAACAACCACTAGTGCCATTAATGGCAAGATGAGGAAGAGCAAAAACAA
TTCTCACGTCAAGGTATTTCCCTGAAGATTTTGAAGTATACGGGAAACTGGGTAGGCAGACAGTTTCTTCA
GCTATGTTTCTAGGTTATAAGACAGACAGAAAGAGAAACATCAGCTTTGTCTTTTCCCTGAGACCTACAGC
CAGCTATTTTATGGAAGTTTGGCCGAAGGAAGATACATATTTACTGTTTGTGTCTGCATTAAGCTTAAAAT
CTAGAGTTAAAAATCCGGGAGACTTTGGGTTCACCTATTCCAGACCTCTCATGTGATATATAAGGAAATTA
TGGCCCCCAAATGTGAAGACTTATTTCTAATAATCAAATGCTATGAGAGTTATTGGAAACCGTTATGGTAA
ATCCCAAGTAAAAGAAATTTATTTTTATACCTATATTTGGAAATGTACTATTCCAGCCCCTACTCTGTAAG
TT

The following amino acid sequence <SEQ ID NO.122> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.12:
LTEGLEYISKYRYKNKFLLLGIYHNGFQLSHLIIRNKSSHLGAIISLYITEVWNRTQSLPDFLILSLMQTQ
TVNMYLPSAKLPNSWLVSGKRQSCFSFCLSYNLETLKKLSAYPVSRILQNLQGNTLTELFLLFLILPLMAL
VVVYGHVAKKLWIHNAVDDISIHTYIWQHGEKKETLKMLMTMVLVYTISWLPLNLYLVLPCREFISSHNGL
CFFFHWLAIS

The following DNA sequence nGPCR-2043 <SEQ ID NO.13> was identified in *H. sapiens*:
TTTATTACGGCCCAATAGGAAGTTGAAACAGCACCTTCAAGGATTAAAATTTATTATATAAAACCGAATTA
ATAAAAGCGTGATTATCGACACCACATCTCCATTTAGCAACCCAAAAGTTCTTCCTGTTCCCAAATCTGAA
AAAAAAAAAATTCGTAAAAATGCCTTACGATGGATGACTACAGCAGACGGGCTGTTGAGGGCTGCCTCAGC
TCTTCAGCCCAGACCAGTGACAGAGCTACCAACACTGCTTCACCTCCTGCAGAGGTAGAGGTACAGGCAAT
GAGAGGAGGGGGTCAGGGATATTTTTTAGCCCTTTCTCATCCTACCCTCATGCCAGTCCCAGCTTTATCTA
CCCTTGAGTCATATTAAGCCATTCAAGGATGAGTGGATGAAGTTTTTAATCAGGAAAAAATACTTCCATGC
CCCCCAATTTGAGAGTAAGAAATAGAAAATGAGGCTATTGTGGGTGTCATTTCTAATTTCTGGACCTCAGC
CTGTACCCTGGGGTAAGTGGAAGTGGAAAAAAACTACAAGAAAACAGAAAGGAGTGGTGGGGATTTGTAAG
GCTTGGATGAGATAGTATATATTAAAGGGGAAAACTTAATTACTTTACCCTTA

The following amino acid sequence <SEQ ID NO.123> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.13:
FITAQEVETAPSRIKIYYIKPNKRDYRHHISIQPKSSSCSQIKKKNSKCLTMDDYSRRAVEGCLSSSAQTS
DRATNTASPPAEVEVQAMRGGGQGYFLALSHPTLMPVPALSTLESYAIQGVDEVFNQEKILPCPPIEEIEN
EAIVGVISNFWTSACTLGVEVEKNYKKTERSGGDLGLDEIVYIKGENLITLPL

The following DNA sequence nGPCR-2044 <SEQ ID NO.14> was identified in *H. sapiens*:
TTTATGACCTTAAAGCATTTAGCAAACTTAATATCTGACCTACATAATTTAGTCTAAATGTTTTTATCAAT
ACTTTTTGAAGCTGTTTTTATTTCCCAAAGATTACTAAAGTTACATAAACTAAAAGGTATTACAGTTTTTA
TTTTGCTTTCAAGATATTTAAGTGTTTATTTTTGTTTAAGCCAATTAATTACAGCCCTTTTACATAAACAT
TACCCACAATACATATATAGCTACACAGAAAGACAGAAGAAGATTACTGCAGTAATTGCAAGATTTTTTAT
TTGTCAGTTTTTAAGTTTCTTAATTGGATTACTGGCTTTAGGGTGGAGCCCTTGGAAAAGCAGAGCCAGGA
AAGGAGTCTCTGGTGCCTCCTGTTTTTCCCAAGGAGCTCAGGCTCTAAGAGCTTCAATATCTGCTTTTAAT
TAAACTGATTTTTAACCATAGCACTCTTTAATAAAAGTTCTTTTAGAATTTCTTATGCCAAACAGCCAATA
TTTCTGGTTTTTGAACTTTATCAAAGGTAACCTCCCAGGTGCTTAGAGAAGGAAAATTTAAGACAGTCCAA
GGAGGAGAAGAGAGTAGA

The following amino acid sequence <SEQ ID NO.124> is a predicted amino



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acid sequence derived from the DNA sequence cf SEQ ID NC.14:
FMTLKHLANLISDLHNLVMFLSILFEAVFISQRLLKLHKLKGITVFILLSRYLSVYFCLSQLITALLHKHY
PQYIYSYTERQKKITAVIARFFICQFLSFLIGLLALGWSPWKSRARKGVSGASCFSQGAQALRASISAFNT
DFPHSLIKVLLEFLMPNSQYFWFLNFIKGNLPGARRKIDSPRRRRE

The following DNA sequence nGPCR-2045 <SEQ ID NO.15> was identified in *H. sapiens*:
TAGTTGTGAAATCGCTATGTAATTTATACAAATATTCAGTGTTTTGTCATATTCCTCATGATCACATATCA
ATTCAGTACATAGCAATGTAGGGATGAAGTTTAGTACTCTAAGCTCACTCATTGATACAAGGATTTAGTGA
GCACCTAGAATAAGACCCAGCACAAAGGTAGCACTCAATGAATATTTCAGGATAGATGAGGAGATAGATGG
ACAGATGGATGGAAGGAGGGAAGGAAGAACAGAAAGCAAATATGAATAAATGAATGACCACAACCCATAAA
AGACTGTATAGAATGAAACAGACATTCTGGCCTGCCAGTACTTTTGAAACCTCTTAAATTTTAAAACTCAC
AAATGCATACTGCACAAATGACCCATTCAGGTTCTGTGAGCCTGAGCTCTCTTGAATACTTGACTGTCTTA
TGACAAGTAAGTGTAGATGAAGCTGGCCCTCCTCTTGAATGCCCTGAGGCTCATCTACCCACATTTATACT
TGGTTTTGTCCTTCAAATCCATTCAGGTAAGCCCTATAATGAAAT

The following amino acid sequence <SEQ ID NO.125> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.15:
FHYRAYLNGFEGQNQVMWVDEPQGIQEEGQLHLHLLVIRQSSIQESSGSQNLNGSFVQYAFVSFKIEVSKV
LAGQNVCFILYSLLWVVVIHLFIFAFCSSFPPSIHLSIYLLIYPEIFIECYLCAGSYSRCSLNPCINEAST
KLHPYIAMYIDMSGIQNTEYLYKLHSDFTT

The following DNA sequence nGPCR-2046 <SEQ ID NO.16> was identified in *H. sapiens*:
AGGAGAGTCTGTGGAGAGAGGGGAAGTGGTTGGCCCAGACAACATTGAGTGAGTTCTACACATCGTTTGTG
GGATGATGATCCCCATTTTATGTAATATTTTCCAAGGATAGAAAAGTACGGAATAATTCTGCAGCTCATTG
TGTGGCTCATAACTCAAAGGTTACTACAACCTTTATCTCCACACCAGACAAGGACAGTAAAGGAAAACAAA
ACAACCACATGTCATGGAAATACACATTTATACACTTACATTATCTTTAAAAATTTAGCAAG

The following amino acid sequence <SEQ ID NO.126> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.16:
RRVCGERGSGWPRQHVSSTHRLWDDDPHFMYFPRIEKYGIILQLIVWLITQRLLQPLSPHQTRTVKENKTT
TCHGNTHLYTYIIFKNLA

The following DNA sequence nGPCR-2047 <SEQ ID NO.17> was identified in *H. sapiens*:
CTTATCTGGATTTTTGTGGTTTTTAGTGTTAGGTTTACCTACTTTGTCTAAATGTATAGGATTATATTTAT
ATTTAACATTTTTCATGTTATTTCCAGGAGTGGTTTGGATCTTTTGTTTCATCCAGCTACTGCAAAACCTT
TGTCATGGCAACATTCAAAGATTATTCAGGCATTCATGAGTCAGGGCGAGCACAGACAAGCCCTCAGGATA
TATTCAGACAATGAAGCCAACAGTGTCCAGTGGTAGCGATGTTATCCTTCACCTCACTGTTTTGCTTTTTA
ATAGGTAAGTACATCTTTTGAAACTATAAAGTCTTTATCGTATCTGTTAATAAAATGGAATTGATGAGATA
GACAGTGGCAATATACAATTGGCCGTTAAGTCAGTAAAGTCAGTCCTTTGTATTAGTGGGTTCTGCATCAA
ATTCAGATTGAAAATACAGTGTTCATGGGATGTAAAACCTGCATATATGGAAGGTCAGCTTTTCATATACA
TGGGCTCTGCAGGACCAACTTTGAAATTTGAGTATGTGTGGATTTTGGTATCCATGGGGATCCTGGAACCA
GTCCCCCAAGGGATACTGGAGGGACAACTGTATAATATTTTACTTCTGTTGCA

The following amino acid sequence <SEQ ID NO.127> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.17:
LSGFLWFLVLGLPTLSKCIGLYLYLTFFMLFPGVVWIFCFIQLLQNLCHGNIQRLFRHSVRASTDKPSGYI
QTMKPTVSSGSDVILHLTVLLFNRVHLLKLSLYRICNGIDEIDSGNIQLAVKSVKSVLCISGFCIKFRLKI
QCSWDVKPAYMEGQLFIYMGSAGPTLKFEYVWILVSMGILEPVPQGILEGQLYNILLLL

The following DNA sequence nGPCR-2048 <SEQ ID NO.18> was identified in *H. sapiens*:
CGATGAATACAAGAGATACAGAAACTGGGAGAGGGAACGTTATTTCAATCTGATGGGCCCTGGGGAAGGCC
TAAGGAGAAGGATGGATTTTGTGGAGGTCTCTAATATTTGGCAAAATTGGTAGTAGAAAGATGTTGCAAGG
AGAGCATTCCTAACATAGGAAATAGCATGGTCAAAAGTATGGAAAAGGGAAAATATGAGGGACATCGAAAG
TGAACAGTGAATAGTTTGGCTTCTTGAGCATACAGTATCCATGTGTTTATAAGCAAGAGATGAGGACTTAG
TGAAAGATAGATACTGAAAAAGTTTGACCTATATACTGGACAGCTTTGGATATCAGGCTGAAGAGTTGTGT
TTTACTGGTGTGCCCTGTGTGTTTTTAATGATTGAATTTGGTCATAGAAAACAGATGGCAAAGGCAGGATG
AAAGAGGAAGAACTGAAAGTCAAGACAATGAATTAGGAAACTACTACAATAATGACAGGCAGGCCGAGGCA
AAGCAGTGGCTGTGCTCTAATATAAGGAAAAAAGTAAGAGTGATAGTCT

The following amino acid sequence <SEQ ID NO.128> is a predicted amino



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acid sequence derived from the DNA sequence of SEQ ID NO.18:
DYHSYFFPYIRAQPLLCLGLPVIIVVVSFIVLTFSSSSFILPLPSVFYDQIQSLKTHRAHQNTTLQPDIQS
CPVYRSNFFSIYLSLSPHLLLINTWILYAQEAKLFTVHFRCPSYFPFSILLTMLFPMLGMLSFQHLSTTNF
AKYRPPQNPSFSLGLPQGPSDNNVPSPSFCISCIH

The following DNA sequence nGPCR-2049 <SEQ ID NO.19> was identified in *H. sapiens*:
ACAGGATGACATTTTCTGGATATGCACAAAACTGAAAACATTTCAGATATTTTCTATAATTCTTTGAGTAT
AAAAATTTTCTGGACTATGTACTGTTTCATCTTATCAAATCCCTCAGACCAAATTTATTTAGATACATATG
TTGCATTTACCACCTAATTTCTCTTAAACTTTGCTGTCTACAGAAGTTATTAGCAGGCACATCTGTGTACA
ATATACTGTAAAGTTCTACATTGACTATTTCTTCCGCTCCAAAGCAGGGCCTGGGATGATTACCATTCCAA
GAGTATTTCTACTATATCTATTGTAGACAACACAGAACTTTATCAAAATAATGCTTACTCATTAGCCCTGT
AAAGGCCTCCCACTGAAGTTATCTTTATTCCTGAATACAGTATAAGATCTTTAAGACCTATGGACAAAATA
AGAGATCTACTATATAGCTCACAAAATTGTAAAATTTATATGTATATTTTTTATACCTTTATACATTTACA
TGTCTTTTGGAAGATACTGTGAACACTGATAATTTTAAAGAGGCCTCATTTAGTTTCATTAATGAAAATGA
TATGCATAAGTACTGCACACTTTCCTCTTTACATGCTAAAACTTGAATAATGACAAAAATATGCTGTACAC
TAAGCCAGACATAATTT

The following amino acid sequence <SEQ ID NO.129> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.19:
RMTFSGYAQNKHFRYFLFFEYKNFLDYVLFHLIKSLRPNLFRYICCIYHLISLKLCCLQKLLAGTSVYNIL
SSTLTISSAPKQGLGLPFQEYFYYIYCRQHRTLSKCLLISPVKASHSYLYSIQYKIFKTYGQNKRSTILTK
LNLYVYFLYLYTFTCLLEDTVNTDNFKEASFSFINENDMHKYCTLSSLHAKTIMTKICCTLSQTF

The following DNA sequence nGPCR-2050 <SEQ ID NO.20> was identified in *H. sapiens*:
TAAGCATGTGAAATATTATAAAGCCTGCCTGAAATTGGTCACATGCCAGGCCCTTCTCCCATTACTCACAA
ACCTGGCTAACCACATGCAAAGGAAAGGGCCAGGGCCCAGCTCAGGATGCTCATCACAGCAGAGGTGTGCT
TTGGGCGGTGGCAGCACCAGGTGGGACAGAGGACACACAGAAAGCTCTCAATATTCATGGCCACCAGGAGA
CAGAGACTCACTGTGTCAGAGAAATAGGACACAGGCTCCAGAAACATGGCCACCTGCAATGTCACCTGGTG
ATACAGCATGAGGATTTTCTCCAACAGGATCACAGTTACACAGGAGAGGTTGACCATATCAGCAGCGGCCA
GGTTAAGGACATAGGTCACGTAGGGGCTGCTCCTGACCTGGAAGCAGAAAAGCCAGCAGACCACACCATTG
CCCACCAGCCCACAGAAGGCCACCAGCACTGTCAGGATGAAAACCACCTGTTTGCCCACCAACCACTCGCC
TCCCGTATGACTCATGTTCACTTGTCCTGGGGTCTCTGTCCTGTTGTCCCAATCCAGCTTCCCAGAGAACA
CTGAGAGAAACTGGGCCATGGTGGGCTGCCTTGGCTGCCTGGGCACACCCTGCAAAGACAAAGGTTGGTAA
CTTACCAGGCCTAGGAAGGAGAGTCAGGGTTGCCTTCTGACCTGCTGGGC

The following amino acid sequence <SEQ ID NO.130> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.20:
AQQVRRQPLSFLGLVSYQPLSLQGVPRQPRQPTMAQFLSVFSGKLDWDNRTETPGQVNMSHTGGEWLVGKQ
VVFILTVLVAFCGLVGNGVVCWLFCFQVRSSPYVTYVLNLAAADMVNLSCVTVILLEKILMLYHQVTLQVA
MFLEPVSYFSDTVSLCLLVAMNIESFLCVLCPTWCCHRPKHTSAVMSILSWALALSFACGPGLVMGEGPGM
PISGRLYNISHA

The following DNA sequence nGPCR-2051 <SEQ ID NO.21> was identified in *H. sapiens*:
AGTGTTCCCGCAGGAAGCATCAAGGCCTCGGGCGTTACAGGGCACACCCCAGGGCTGAGCTCCCAGGGAGA
AGGGAAAATGTTTTCACACTGACTGCTGGGCAGCCTGGTACATAGCTCTAGAACCTACTGCTGTGTCCCAA
GTTTGCATATCTTGGAAGGAGTGCACACAGCAGGGAGAGGGGCCCAATAGCAAGAGGTACAGAAGAAGGAA
AGGAGAACAGAGAGAAGATCATCTGGGGTCGAGGAAAAGGAAAAGTGTATAGCTTATAAGCTTTATTTTCC
CCATAAAATCTTGCCTGATTGAGCACATAAACATGCAGGATACCCAGTGAAATCTGAATTTCAGATTAACA
ACACATATGGTTTTCAGGATAAGTATGCCCCAGGCAATATCTGAGACATACTTAGACTCAAGAAAAAAAAA
ATCAGTGTCTATCCAGAATTCAAGTGTAACTGGGTGTTCTGTATTTTATAGGCAATCCTATCCCCACATCT
TGCCCCCCGGGCTATAATGGAAACCCTCAAAGGCTGAGACTGTTTCTGCCATGTCCTTCCTGCATTTCCAT
GTGCCACTTTGCTCTGTAATGTAGCACA

The following amino acid sequence <SEQ ID NO.131> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.21:
CYITEQSGIWKCRKDMAETVSAFEGFHYSPGGKMWGDCLNTEHPVTLEFWIDTDFFFLESKYVSDIAWGIL
ILKTICVVNLKFRFHWVSCMFMCSIRQDFMGKIKLISYTLFLFLDPRSSLCSPFLLLYLLLLGPSPCCVHS
FQDMQTWDTAVGSRAMYQAAQQSVKHFPFSLGAQPWGVPCNARGLDASCGNT

The following DNA sequence nGPCR-2052 <SEQ ID NO.22> was identified in *H. sapiens*:



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GGGGAGTGGTGTTTGGTTTTTGAAAAGAACAGTAAGAGTTATCATTGGTTCAAAAATTGCTTCTTTTATTG
TTTTGTTCATGATTATTTAGAAGGAATTTGGAAATCTGATTGAGCAAAATAAAGGACAGGCAGCTTTCCAT
TTAAGGCTATGGATAATATCCCCCTGTGAATGAAAATGTATTCCTGCATACAGATTTGTAGGATGGTGTTT
ACTCAGTATCATACAAAGCACTTGTGCAATGTGGGTCAATAAACATGTGCAGAACACTTAGCTTGACAGGT
TTTATGTAAATCCAAAAAGAAACACTGGATGTTCTTATTTCACTTAAAGGAAATTAAAGCAACTGTTTTAT
ATGCCCAAAACTTGTGTGTAATTGATAGACTCACAATACAAATATTTCCACTTGGAATCAATGTAAAAATT
ATGCAAAATTGCAATAAAAACTTTAAATGAATGCTACTTGGCTTAGTTTACCTTAGGCTAGTGCTTTAAGT
TTAATTCTGCACTAACT

The following amino acid sequence <SEQ ID NO.132> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.22:
GEWCLVFEKNSKSYHWFKNCFFYCFVHDYLEGIWKSDAKRTGSFPFKAMDNIPLMKMYSCIQICRMVFTQY
HTKHLCNVGQTCAEHLAQVLCKSKKKHWMFLFHLKEIKATVLYAQNLCVIDRLTIQIFPLGINVKIMQNCN
KNFKMLLGLVYLRLVLVFCTN

The following DNA sequence nGPCR-2053 <SEQ ID NO.23> was identified in *H. sapiens*:
TTATTTTTATTCTACTTTTCCTTTACCTCAAACATTTTATGTTTTCTTGAAGCAAATTATTTAAGTGTTT
CTGTCATCCTCTTCATATCCTTTATTGAAAAATTTGATGAGAGGATAAAATTAGTAACTATAATGCCAGAT
GGATATTGAATGTTTGCTATTCTTTCACCATTCTATTTCTTTATATATGAATATTTTGATTCAGCATAAA
TTTTTCACATTTATAACATGGCCGAGAAAATAGTTTGTATTAAAATCATAGCTGGTGCAGATTTTGATTTA
TAATAAAACATACATAATATTTTAACCAAATTATTACAATAAGTTTTCTATCAAGTTTTTATATAAGGATA
ATTACTAATTATCAATCAAATATAGTAAATGACAATAAATAGAAAAAAGTTATAAAGTAGCTCACTTTCTG
TGTTTTCCTTTTGTTTTTGTTTTGCTTTGTTTTGTTTTTGAGACGGAGTTTTGCTCTTGT

The following amino acid sequence <SEQ ID NO.133> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.23:
LFLFYFSFTSNILCFLEANYFKCFCHPLHILYKIEDKISNYNARWILNVCYSFTILFSLYMNILIQHKFFT
FITWPRKFVLKSLVQILIYNKTYIIFPNYYNKFSIKFLYKDNYLSIKYSKQIEKSYKVAHFLCFPFVFVLL
CFVFDGVLLL

The following DNA sequence nGPCR-2054 <SEQ ID NO.24> was identified in *H. sapiens*:
CTATAAACTAGGTGGCTTAAAACAACAAAAATTTATTCTGTTCTAGTTCTGGAGGCTAGGAAGTCTAAAGG
AAAATCAAGGCGTCAGCAGATGGAAGCCCTAGATAGTCTAGGGAGGAATTCTTCATTTTTTCCTTGCTTCT
GGTGGCTCCCAGCAATCTTGGTATTCCTTGGTTTGTAGCTGCATCACTCCAATTTTTGCCTTCATCTTTCC
ATGAACTTATTTCCTGTGTGTGTCTCTGCATCTCCTCTCTTTTTATGGGGTGCCAGTTATTAGATTTAAGG
CCCACTCTAACCCAGTATGAGCTCATCTTAACTTGATTACATCTGCAAAGACCTTATCTCCAAATAAGGTC
ACCTTCTGAGGTTCTTGGTAGACATACATTTTGGGGGGATACTATTCAACTCATTACACCACAACTCCCCA
AACTAGAGAGATAGGCAAATACAGAGAATCACAGGTTACAGGGAGCAGAAGCCTCTAAATGCAATACCTGA
TAGAAACACTTAAACAATAATTGACACATT

The following amino acid sequence <SEQ ID NO.134> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.24:
INVANNKNLFCSSSGGEVRKIKASADGSPRSREEFFIFSLLLVAPSNLGIPWFVAASLQFLPSSFHELISC
VCLCISSLFMGCQLLDLRPTLTQYELILTLHLQRPYLQIRSPSEVLGRHTFWGDTIQLITPQLPKLERANT
ENHRLQGAEASKCNTKHLNNNHI

The following DNA sequence nGPCR-2055 <SEQ ID NO.25> was identified in *H. sapiens*:
TCAGCAAGGATGAAACAGGGTATAATCCAGGAATTCAAGGATAATATAGAAAACTTTAAAGAAAAAATAAC
GTAAGTAGGTGCCAAAATGTCATTTAAAACTCATCCTGGTAAAAAAAAAAAAGATTACAAGATTAGAAAT
AGACTTTCTTACCCCAATGATGAGCATGTAATCATATATTCAATTAAAATATTTATTGAGCATACATCCAT
TTTCCTTGCTAGTAAAAATTAGGAGCATTCACATTAAAATCAGAGATAGGTTAAGGATGTCTGCTATTCAG
AGTAATTACTATTGGAAAGGAGGAGGCAATATTATAATTATTTCTATATGGTATGATTATATCACTAGAAA
ACGATGAGAATCAACTCAAATTACTCAGAATTTATAAAAGCGCAACGAAATTACCAGATAGAGGTAAATAT
AAAAAAACCCATAACTTTTCTGTATATTGATAAGAATTTTAGAGATAAAAAGGAACAGATTCCATTCTTTG
TCATCATCATCATACCACAGCAAAATGCAATTAAATACCTATGATGAATCTTTACAAGGAATGCAGAGAAT
TTATATGGAAAATAACAAAACTTCACTGGCAGATGTAAGCTATTTGAATAAACGGTAATAAATGCTATGTT
CTTAGACTGAATGGGTTTGTTGCTGTTTTGAGATGGAGTCTTGCTCTGTCATCCAG

The following amino acid sequence <SEQ ID NO.135> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.25:
GQSKTPSQNSNKPIQSKNIAFITVYSNSLHLPVKFCYFPYKFSAFLVKIHHRYLIAFCCGMMMMTKNGICS



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| |
|---|
| FLSLKFLSIYRKVMGFFIFTSIWFRCAFINSEFELILIVFYNHTIKLYCLLLSNSNYSEQTSLTYLFCECS FLLARKMDVCSINILIEYMITCSSLGESLFLILSFFFFTRMSFKHFGTYLRYFFFKVFYIILEFLDYTLFH PC |
| The following DNA sequence nGPCR-2056 <SEQ ID NO.26> was identified in *H. sapiens*:<br>GTCTACCTTCCTCTCTCTTTTCTGACCTGTCCCCTCTGTCTCATTGTTCAAATACTGAGGAGCTCAGGATA GAATCCAGGCCCTTGGCGTTTACCTTCCCCATTCTTTCCAGCCTCCTGTCCGCCTCTCCCAATATTCCCTG AGCACACCTGGTCCCCACAGGACTCAGCACCCGTGTAGTACTCTGTCTTTCATGTATAATGTTCTCCTCTG TTTTCTTTGCTTGGGAAACTCCTAAACATCTCTCAGGACAGAGTTCTAATATCTCTAAGAATGCTTTCTCT AGCAACTCTCAATGTCCTTAGAGCACTTGGTTCATACTTATGTGAAATAACTTCCCTTACATTACACATAT TTATGGATCCATTTTTTCTCCTAATCTGTTGGCTGGACAAGGGCAGGCACTACATACATCTTCTTCATCTT TGGATAGCCAGAGTAGGTGCTCACTAAATGTTTCTTCTAAACGTTTTATTTTAGATTCAGGGAGCACATGT GCAGGTTTGTTACATAGGTATATTATGTGATGCTGAGGTTTGGGCTTCTTGGGATCTCATTGCCCAACTAG TGAGCATAGTACCTGAGAGGTAGTTTTTCAACCCTGGCCCTCTCCCTTCAATAAATATTTCTTGAGTGACC C<br><br>The following amino acid sequence <SEQ ID NO.136> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.26:<br>VYLPLSFLTCPLCLIVQILRSSGNPGPWRLPSPFFPASCPPLPIFPEHTWSPQDSAPVYSVFHVCSPLFSL LGKLLNISQDRVLISLRMLSLATLNVLRALGSYLCEITSLTLHIFMDPFFLLICWLDKGRHYIHLLHLWIA RVGAHMFLLNVLFIQGAHVQVCYIGILCDAEVWASWDLIAQLVSIVPERFFNPGPLPSINISVT |
| The following DNA sequence nGPCR-2057 <SEQ ID NO.27> was identified in *H. sapiens*:<br>TATTTATTTACACAAAGATTTTGAGAAATTAAGCAATATTGAACTTGAGGTCACTCCCCCTAATGAGCCTC TATTGCATGTATTCTCTGATGGTGCTTAAACCAGAGCCAGATAGGATTTAATAGACTAAGCAGGGGAGAGA CATAACAGTTCTTTATGTGGGGGAAGGAGAGAAAGAGAAAAACAGAGCGGGGAATAAGACAGAGGACAAAA ATGATACATACAGAAGGGATTAATGTAATAGTTCTCTTTTTCTCTGCATTGAGGTAGGACACAGAATTACT TAGGCCCTACGGTTTCACAGGACCATAGAGAAAGCATATCATCCAATGAATGAATCCATTAACAGTGGAAG TTGTACAGATCTGTAGCAAAAATGATGGTAACAAGACTATTAGCCGAGAAAATAGGTGCAACCCATTTAAG CGTGTATGTGTGTATTTATATATATAAATATATATAAATATATTCATATATATAAATATATTTTTATATAA ATATATTTATATAAATATATTTTTATATAAATATATTTATATAAATATATTTATATAAATATATTTATATT TTTATATACATATTTATATAAATATATAAAAATATATTTATATAAATATTTATATAAATATATAAAAATAT ATTTATATAAATATATTTATATAAATACATATTTATTTTATATAAATATTTGTATATAAATATATATAAAT ATTTATATATTTATATATAAATATGTATAT<br><br>The following amino acid sequence <SEQ ID NO.137> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.27:<br>YTYLYINIIFIYIYIQIFINKYVFIIYLYKYIFIYLYKYLYKYIFIYLYKYVYKNINIFIIYLYKYIYIKI YLYKYIYIKIYLYIIYLYIFIYINTHIHAMGCTYFLGSCYHHFCYRSVQLPLLMDSFIGYAFSM VLLKPGLSNSVSYLNAEKKRTITLIPSVCIIFVLCLIPRSVFLFLSFPHIKNCYVSPLLSLLNPIWLWFKH HQRIHAIEAHGEPQVQYCLISQNLCVNK |
| The following DNA sequence nGPCR-2058<SEQ ID NO.28> was identified in *H. sapiens*:<br>GGTGTAACAACACTCCAGGCAGAGGAAAGTAGCCATGTTTGAAGGCTCTGAAGCTGGAAAGAGCCCAGCCT GTTTAAGAAACTGAAATAAGGCCAATGCGGCTGCAGCTCAATGAACATGGAGAAGAATGTCCTGAAATGAA GTTGGCCAGATAGGGCAGCAGTGAGATCACGCAGGATCCCGAAGGTTATAGAAAGAATTTGGGATTGTACC ATAAGTGCAATGGGAAACAAATGAATTTCTTAAATGGGAATGGCATAATAAACTTTATATTTTTAAGAGCT CTCTCTAGGAACTGTGCGAAGAATATATTGGACAGCACAAGAAACAAAACAGAAGTCCTGTCAGGTGTATT CCAGATGGAAGATGGTGGTGGCTTAGATTAAAGTAATGGCAGAACAGATGATGAGGAGACCATTTGAAGTG AAATTGACACAACTTGAGTTTTATAGTAAGTTTGAATTTAGCTTCTATTTCCAAATTCCTCAAAGAGGTTA ATACTTAAAATCCTGAGCTAAAGTTAACCTAGGCAGGTCTCTTCATAAAAGCTCAAGAGCTAACTGACTAT GATGAAATATCGTTTCACACCCACTAGGATACTTATATTCAAAATATAGTAACAATAGTTAGTGTGGGTGT GGAGAAA<br><br>The following amino acid sequence <SEQ ID NO.138> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.28:<br>FSTPTLTIVTIFIVSWVNDISSSVSSAFMKRPAVNFSSGFVLTSLRNLEIEAKFKLTIKLKLC QFHFKWSPHHLFCHYFNLSHHHLPSGIHLTGLLFCFLCCPIYSSHSSRELLKISLLCHSHLRNSFVSHCTY GTIPNSFYNLRDPASHCCPIWPTSFQDILLHVHAAAALALFQFLKQAGLFPASEPSNMATFLCLECCYT |
| The following DNA sequence nGPCR-2059 <SEQ ID NO.29> was identified in |



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*H. sapiens*:
TTTTCCTGGCTCATGCTGACCTTAGTACTTTCACCCACATTCTTCCCCACCTCCTGTAGCCATCAGGGACC
TAAGGAAAAAATCCTCCCCCACCCTGGTGGCTCTTGTCTTAGTTCCCCACATGGTCCTTCCTTGTGCCTTCA
AAGTGCCTTCATTGGCCCTGAGGAGGGATGGCATCCTGGCCCTGAGCTTCTGTCACCTGTGCATGGAAACC
CAAGTCCTCACATGCCTTGGCAGGGTATCCCCTGGGAGGCTTGGGTCCAGTCCTGCTCTGGGTGACTCGGG
CACCTGGCTGGCAGCTACCCAAGCACACTGGCCTTCTGGCTCTCATTCCCAATCCCCTTCCCAGGTCCCAG
CTACCCATGCTCATTCAAGCAGCCTCCCATTTTGCATTGTCTT

The following amino acid sequence <SEQ ID NO.139> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.29:
FSWLMLTLVLSPTFFPTSCSHQGPKEKILPTLVALVLVPHMVLPCAFKVPSLALRRDGILALSFCHLCMET
QVLTCLGRVSPGRLGSSPALGDSGTWLAATQAHWPSGSHSQSPSQVPATHAHSSSLPFCIV

The following DNA sequence nGPCR-2060 <SEQ ID NO.30> was identified in *H. sapiens*:
AGTTTATGTATATATGTTGACAGGACTACATCCAATTGAATAGTTAAATGCATTGTAGTCCTCAAGTCTTG
GTAGAAGACTTGAGAATTTATTTTTTTAAATCAAACTCGTATTCACTTATATTCATGGCATTAAACAAAG
AACAATGGAGTGCCCAAGTGAGTTTTTGGTCTGTTTGCCAAAGTGATCACTTTTGTTTCTAAACATCTTC
TCTCTACAAAGCCTTCTTCCTCTAAGTTCTTTGATCAGAATGCCCTGTACCTGACACACTACTACCCAGAT
AGGCTGACATGCCTACTGTGTGCCTTTTTCCTCCCTAGATTGAGAGCTTCCATTTATGGATAATAATTGTA
GCTAATATTTGTTGAAGATTCTCCTATCTGCCATAGATGCTTTACATGGATTATTTCATTAACTCACTAAA
CAATCTTTTAAAGAGGTGCTACTGTGTCCAGAATTAGTTCCTTCTGGTGGGTTCTTGGTCTCGCTGACTTC
AAGAATGAAGCCGTGGACCCTCGCAGTGAGTGTTACAGTTCTTAAAGATGGTGTGTCTGGAGTTTGTTCCT
TCAGATGTTCAGATGGGTCTGGAGTTTCTTCCTTCTGGTGGGTTTGTGGTCTCGCTGA

The following amino acid sequence <SEQ ID NO.140> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.30:
SARPQTHQKEETPDPSEHLKEQTPDTPSLRTVTLTARVHGFILEVSETKNPPEGTNSGHSSTSLKDCLVSN
NPCKASMADRRIFNKYLQLLSINGSSQSREEKGTQACQPIWVVLCQVQGILIKELRGRRLCREKMFRNKSD
HFGKQTKKLTWALHCSLFNAMNISEYEFDLKKINSQVFYQDLRTTMHLTIQLDVVLSTYIHK

The following DNA sequence nGPCR-2061 <SEQ ID NO.31> was identified in *H. sapiens*:
TATGCACATGTGTCTATCACACTTTTGTGAGTGTTTAAGTAGAATTCATTCACATGCATACACACTTTCAT
TGTACCATTCTACGTCTAACAAAAAAATGTTGCATTCAAGGGTACAAATAATTGAACGTAATAGTTGTTCT
GAAATTGTGCTCAAAAGCATATAGCATAAGAGAAAGAAGCCAGTCACAAAAGGCCACATATTGTATAATTC
CATGTATATGAAATGTCCAGAATTGATAACTTCACAGTGTTGAAAAGTAGATTAATGGTTGCCTAGGGCTG
GGGGCCAGTGGGAGGAGTGACTGCTAATGAGTGCTGGTGTCTTTTTGGGGTGATGGCTGCACAACTCTCTA
CATATACTAAAAACCATCAAAATGTAAAACAAAACAAGCAAACAAACTACATTGCTTTGCAAAATCAATTT
CTGAATCTTCGCTGAACCCTCCCATCACCTTCTCTAAGGGGAGTTTGTCCCTTCCACAGGACAGCACTGCC
TTCAAGGCCTTACCAGGGGTGGTCTCCCATGCCCTCATACTGCTGGGGCT

The following amino acid sequence <SEQ ID NO.141> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.31:
APAVGHGRPPLVRPRQCCPVEGTNSPRRWEGSAKIQKLILQSNVVCLLVLFYILMVFSICRELCSHHPKKT
PALISSHSSHWPPALGNHSTFQHCEVINSGHFIYMELYNMWPFVTGFFLLCYMLLSTISEQLLRSIICTLE
CNIFLLDVEWYNESVYACEILLKHSQKCDRHMCI

The following DNA sequence nGPCR-2062 <SEQ ID NO.32> was identified in *H. sapiens*:
ATGAAACTTCCTCACGGCACCAGGGGGTCCTTATGTACTGGCCCCTAATCCAGCTAATCCTGATGGCAACA
AAATCATGAAAGTGGCCCCCAGTGACGTGAGTCTCCCTGCACAGATGCAGAGGGAAGGAACAGTGCAGGAG
ATAAATGAGGCCAGCGTGGTATTCACCGGAGGCCAGGGAGCCTGCGTGCGAAGGTGGAGACTCGCATTGTC
TTCTCCCCCATGTCGGCTCAAGTGGGAGGCCAATGAAGAGAGGCCCAGGCTGGATAATGGCAAGAAGACTG
TTCAGAGCTGAGAGGTGATGTCAGCCCCACAGAAGCTGAGAGAAGGAAACTGGGGTTAATGTTATGCAATG
CCTTGAGTGCTGTGATGGAGAGCCTGCCGTGGAAGCACTTGGGTTTTGTTGTTGTTGTTGGGTTTCTTTCT
GTTTCTATTTTTTTAATGAAGACTTCAGGAGGTTTCAACTAAGCTTGATGAAAACACGCTGTGTTGGTTCC
TGGGTTCTGCTGCCTGCTGCTGCTGGAGTGTGGCCTCTGAGCCAGCGCGCGCTCGTCATCACACCTCTGGG

The following amino acid sequence <SEQ ID NO.142> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.32:
ETSSRHQGVLMYWPLIQLILMATKSKWPPVTVSLHRCRGKEQCRRMRPAWYSPEAREPACEGGDSHCLLPH
VGSSGRPMKRGPGWIMARRLFRAERCQPHRSEKETGVNVMQCLECCDGEPAVEALGFCCCCWVSFC
FYFFNEDFRRFQLSLMKTRCVGSWVLLPAAAGVWPLSQRALVITPL



BNSDOCID <WO 0162924A2 I >

The following DNA sequence nGPCR-2063 <SEQ ID NO.33> was identified in *H. sapiens*:
AAACAAAATAGCACTTACCATGAGTCTATACTCCAAATATGTGTTCAATACAAACTGTAAATATCAACACA
ATAATGATTATTTTTAAAAATACAACCAGGAAGTGAGCATTCCGAAGTTCTGGGGAGAAGCCAAGTGCTGA
GGTATATCTGGCTTGCTGCACAATGGTGTCAACTCTCATTTTTCTTAAAAGGGGATAAAAGGGAACCTGGT
CTTCTTATAAAGAAAACCCACTGACTTCATGAAAAAGTCACATCTCCCTTGGGTATCTATTTTACCTATTC
AAATGACTAGCAAGCTTGCTATTGAAAATGCTGAGAAATATTAATACAAACTCTCTCAGGTTAAAGATATA
AAGTCTGTGAAAATACATACAGCCATATGATTAACACAAACAGTCCTTTTTTTTAAAAAAAATGGCATTTT
TATTTGTTATATTGGGTAACAGGCAGAATAAAAAGAAAATAAAGCAATGCATACAAATGAGGAAACTGCAT
TCTGTATTATATAAAGATTTAATTTTATCATGAGCTTTGGAACATTCTATATAGGAAAAAATTGTTAGTTT
TTTTTTCATTTTTAGTCTCTGAAAGAGGATCCTGTATTAATCTAAAAACCTAAATGCAAACTTGTACCAGA
GTT

The following amino acid sequence <SEQ ID NO.143> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.33:
LWYKFAFRFLDYRILFQRLKMKKKLTIFSYIECSKAHDKIKSLYNTECSFLICMHCFIFFLFCLLPNITNK
NAIFFKKKDCLCSYGCMYFHRLYIFNLREFVLIFLSIFNSKLASHLNRNRYPREMLFHEVSGFSLEDQVPF
YPLLRKMRVDTIVQQARYTSALGFSPELRNAHFLVVFLKIIIIVLIFTVCIEHIFGVTHGKCYFV

The following DNA sequence nGPCR-2064 <SEQ ID NO.34> was identified in *H. sapiens*:
ACAGTCCTGCAAAATGCAAGCACCAGGGGATCCGATTCTATTTATTCTTGTGATACATAGTTCAGTTTTGG
CAAACTAATGTTTTGGGAACAGTGACCAATGAATTTGTCTTGTCTTTTATGATATAATCTTCAAAGACAAA
TATTAGAAGCAGTATGTTTAGAAAGAATTAGAAGAGCAGTGAACTCCAACATCCAAAGTTTCAAATGTCGT
GACTGTGTGCTGCCTATGCTAACTGTCTGGCATTTGCAATATGGATGCTTTGCTTAAGACAAAATGCTTTC
CTAGTCAAAGCCCCAGAAAATTGTCTGCTATCACAGTATTGACTGCTGTCTGTCAGCAAGTATTTTTTCCT
TGCTTAGAAACTTCATCAAAATGCCTTCTCAAAAATCAGCTGTCACCTCCCCTTCTATTCAGCTAACCTCA
CACTGTATCCTCCTTGGGATGCACACTTACTAATCCTCTTGAGCCAAGTTAGACCAGGTTTGTGGGGACGT
CAGCTCTTGCCCTCT

The following amino acid sequence <SEQ ID NO.144> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.34:
RGQELTSPQTWSNLAQEDVCIPRRIQCEVSIEGEVTADFEGILMKFLSKEKILADRQQSILQTIFWGFDES
ILSAKHPYCKCQTVSIGSTQSRHLKLWMLEFTALLILSKHTASNICLRLYHKRQDKFIGHCSQNISLPKLN
YVSQEIESDPLVLAFCRT

The following DNA sequence nGPCR-2065 <SEQ ID NO.35> was identified in *H. sapiens*:
TTACCCCTGGATTACAGGAAGGGCATGTGCTAAAAGCCTCTTTGGAGACCCACATGGCCCTCAGATGAGCA
ATTGTTCAGATTCCTTTTCTTTTTCTTTTCCATGGGAATAAGCTTTCCTCTCTCCAAAGTACATGTTTTAG
GCTTTTTTATTTTCTTGCTACTCCCAAGGACCTGGTGATATTTTTCTTTACCATGCATTAAACAGAATCTG
TGAGTCTTTTCTGGAAAAAAAAAAGGCAGGAGGGAACATACTAGTTAAAAAGTTTCTGGGTACACTACCAA
GATGTACCTATTTATTGATATACAAATGGCATAAGTTATTGAATGCTTGCTATAGGCATTCTCTAAGAACT
TTGTAAGAATTGACTTACATGAGCTACTTCATAGCAGTTCGATGATATACATGTTGTTATTATCACCACTT
TACAGATAAGGAAATAGAGACAGACATACTGAATGACATGCTCAACGCCACTCCACTAGCAAGTGGCAGAA
CCAAGCTTGAAACAGCTGGTCTGACTCCGGAGTCTGTGCTCTGATCTATATCACAGCTATTTCTATATGTG
CTATTCTACTAATATATATATTTTTTGAAATACATGAAAAAGTAATTTTAATAGAATGAGATACATATTGGCA
ATATTGAAGTTCTCATACTTTTTGTCCTCTG

The following amino acid sequence <SEQ ID NO.145> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.35:
EDKKYENFNIANMYLILLKLLFHVFQKIYISRIAHIEIAVIIRAQTPESDQLFQAWFCHLLVEWRACHSVC
LSLFPYLSGDNNNMYIIELLSSSCKSILTKFLENAYSKHSITYAICISINRYILVVYPETFLVCSLLPFFF
PEKTHRFCLMHGKEKYHQVLGSSKKIKKPKTCTLERGKLIPMEKKKKRNLNNCSSEGHVGLQRGFHMPFLS
RG

The following DNA sequence nGPCR-2066 <SEQ ID NO.36> was identified in *H. sapiens*:
TCTCATCCCAAGGAAAGAGAGGTATTTCTCCAGCCTGAGTAAAAGAGCACCACAAAGGAACAGGATCTGAG
ACCTGGGAGGATTAAATATTTCCTACGGGGAGTCGAAAATAAGATTGCTATAAAGAGGTTCTCCTACTACA
GGTAGGAGACAGCCTTGAGACTGTGCTGCTTCCAGGAAGAGGGAAGATTCTTAGAAAGGGGGGGATCCCTT
GAGGGCTTGAAGATGAAAAGAAAGAAAAACATGACCCCTCCCCACAAAATCCCTCAAACAAGGGAGTATCA
AAGAATCAGAAAAAGTCACATTAAAGCCCTATTTCTTAAAGAATTGTTCTTTTCTGTAGCAACAAAAGAAA



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GAGATTTTGAACTTAGAACCAAGTAAGCCACTCAAACCCATTCCTCCTATCTCTATGCTTATCTGTTAGGA
AAGTCCAGCTGAAATAGATAATAATAAACATTAAAATAACCCAACATCCACCCAAAGTTAGTTTAAAAAGA
AAATGGAAAATGAGAATCAAAACATTACAGCAGATGAAAACATACACAAACAAAGACATGACACAGGAAAA
CTATAACACAAAATTCCAATAGGGGCAAAAATACTTAAAAAATAAAATTTAGATATTAAAGATCGACACTT
TCTGACAAGTTCAAAACTCA

The following amino acid sequence <SEQ ID NO.146> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.36:
EFTCQKVSIFNIILFFKYFCPYWNFVLFSCVMSLFVYVFICCNVLILIFHFLFKLTLGGCWVILMFIIIYF
SWTFLTDKHRDRRNGFEWLTWFVQKLFLLLLQKRTILEIGLCDFFFFDTPLFEGFCGEGSCFSFFSSSSPQ
GIPPFLRIFPLPGSSTVSRLSPTCSRRTSLQSYFRLPVGNISSQVSDPVPLWCSFTQAGEIPLFPWDE

The following DNA sequence nGPCR-2067 <SEQ ID NO.37> was identified in *H. sapiens*:
ATTTACATATGTATAACATTCCCTTACAGTGCCATATAGCCCCCTCCAAAATTTAATACTTAAACTTTTTG
TGTTTATTTTTCCCCAGTTGTATACAGTCCCCTGAAATAACAAAAGCTTATTTTAAGGATTTAGAAATAAA
TTAAAATCGGAAAAGACTGTCTTAAATAAAGACATATAACTTACCCACAAAGAAGTCAGAGATGGCCAAGT
TAAGAAAAAAATAACTACTTCGATGTCTAAGGTTTTTGTCCACCACAAAAGCTAAAATGACCAAAGCATTT
CCTAGCATTATAGCAAAAGCTACTAAGGACATAAAAAATGCTAAAGTAACACGAGTGCTTAGTGATAAATT
GATTGTGCTATTAGTATCTGGCATCACATCAAATGATGAAGAAGGTCAAATTAGCAAATTAATCCAGCCAG
ACAATTCTGACAAGTATGTTTTCTAATCACATACCTAAAATGTGTAGTCTTCCACTCAAAACAACACTGGT
TTAATCTAATGCTGATCTCATAGTACTTCCTGATTCTTG

The following amino acid sequence <SEQ ID NO.147> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.37:
KNQEVLDQHIKPVLFVEDYTFVCDKTYLSELSGWINLLIPSSSFDVMPDTNSTINLSLSTRVTLAFFMSLV
AFAIMLGNALVILAFVVDKNLRHRSSYFFLNLAISDFFVGKLYVFIDSLFRFFISKSLKAFVISGDCIQLG
KNKHKKFKYILEGAIWHCKGMLYICK

The following DNA sequence nGPCR-2068 <SEQ ID NO.38> was identified in *H. sapiens*:
AAAGTCTAAAATACAGGATAATCATGACCTCCCACCATCCACCACCCTGAAAGTCATTTTATGTCTCCTTA
TATTATTGAACACAATGTCTCAATTCAATGTCGTACACAAAGCCATCCATAATTTGAACAGCATCCTTTCT
CTCCATTCTCCCACATTTAGGTTATGTCCTGGCCCACGCTACCCTTTCATAAGTCTACCAACACTCCACAT
TCTTTCACATCCCCATAGTTTGGATGTGCTATTTAATTTGTCTTCTCCAAGCATTTGTACTTCCTGCCAAA
CACACATACTTTCTTCTCCAGAATAACTCATATTCATTCTTGAAGACTTGATTCAAGTTTTTTCTCCTCTG
GGTGCCTTCTATAAACCTTCTTTCCTCTGCTCCAATTTGGGAAGTGCTGTTCCCTCTATACTCTCATCAAC
CATAGCAGCCTAGCCTACGTCTATTATAGATTTGTCGTACCTTGTTGTAATTAACTGTATGTTTATTAATA
ATGATAGTAATGATAATTTTGGTATCTGTAGGTAATTGAATATAAA

The following amino acid sequence <SEQ ID NO.148> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.38:
KSKIQDNHDLPPSTTLKVILCLLILLNTMSQFNVVHKAIHNLNSILSLHSPTFRLCPGPRYPFISLPTLHI
LSHPHSLDVLFNLSSPSICTSCQTHILSSPELIFILEDLIQVFSPLGAFYKPSFLCSNLGSAVPSILSSTI
AAPTSIIDLSYLVVINCMFINNDSNDNFGICRLNI

The following DNA sequence nGPCR-2069 <SEQ ID NO.39> was identified in *H. sapiens*:
TCATCGAACAAGAATTCCTCATAAAAGAGAGGGGATAGAGGCCTGAAAATTTTAAATAAAGTTCAAACCTT
GTAATTAGTGATTCTAAAATTTAGGTGTGTAAACTTGAGTAAAGTTTTAGTGTCACCTGATAAGTGTGAAG
TAAATGAAGAATCTTGGGCTGTACTCTCCAAGTGTCTCGGAAGTTTTCAAAAACCCATATCCTGGGTAAAA
TGCATTAATGTATGGCTGTGTGATATCCATTTTAATGTTGTTGACAGCTTTGGGCAGAGAATTCTAGCTTT
CCCCTCTCTATATATGTACCCCCTTTCCTCCACAATAATTAATTTTTAGTTGAATCAATGACTGCCCATCC
AAAAAACAAACAAACAAACAAATAA

The following amino acid sequence <SEQ ID NO.149> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.39:
SSNKNSSKRGDRGLKILNKVQTLLVILKFRCVNLSKVLVSPDKCEVNEESWAVLSKCLGSFQKPISWV
KCINVWLCDIHFNVVDSFGQRILAFPSLYMYPLSSTIINFLNQLPIQKTNKQTN

The following DNA sequence nGPCR-2070 <SEQ ID NO.40> was identified in *H. sapiens*:
AAAAAAAAAAAAAAAAAAAAAAAGGGTAATAAGTGGGGAGTAGGGAACACCAGGTGCTTAGTATATACTAT
GGCTTGGTTTGCAAGGAATCTGTCAACATTAAGCACAAGTCATCTATTAATACTATCGTAGTCACAGTAT



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GCCACAAAAAAACAAATAACTCACAACCAACATGGTGTACATTAAACCAGTTACATAATATATACAAACAT
ATATAAATAGTGTCAGATATAAACTAAACATTACACTCAAAAAGAGTTAGAGGTCTCTGCAGAATCATGTG
CTCAAAGAATCTATGACTGAAAGTACATGTTAAATGCAATGCAGGAAATGTAAAAGTGTTAATTATTTAAA
TGTTATACATTTGCATTTGCAGATGTTATTTTATAATAAGCTACTGTCCTTAAAGAATTTAAAATCATCTC
AATGAAGAGCAAAGAGGAAATGAGAAAAAA

The following amino acid sequence <SEQ ID NO.150> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.40:
FFSFPLCSSLRFILGQLIIKHLQMQMYNIIINTFTYPALHLTCTFSHRFFEHMILQRPLTLFECNVFISDT
IYICLYILCNWFNVHHVGCELFVFLWHTVTTIVLIDDLCLNVDRFLANQAIVYTKHLVFPTPHLLPFFFFF
FF

The following DNA sequence nGPCR-2071 <SEQ ID NO.41> was identified in *H. sapiens*:
CCGCCTGCCCCTGTGGCAGTGTCGATGTTGTCTACTTCCCCGTGTGCCTCTATTCTTGGGCTCTGTCTCTG
TTCTCAACACCGCTGTGTGCTGAGCACAGCAGAAATCAGGACATTCACCATTCCACCTGCAGCCTCTGGGG
CCCCTCTTTGCTCTGGCCACCTTACCCTCCTCGGGCCTCCCCACCATTGCACTCACCACACCCCCAACTCA
CCTGCCCCTCCACCTGGAAGGGGATCAGTCCCTGAATCATATGACCTGGGCACGCCCTCCCCCAGTCTGGG
ATGGCTGCTCCTCCTTCCAGGGCTGGTGCTGGGCTCCACCACCTATGAAAGCGCCAGGTTATCTGCTGTGT
CCACGTGTGTCTCTGTCAGTGGTGGTGGGGGTGGGGAGGTGTCT

The following amino acid sequence <SEQ ID NO.151> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.41:
PPAPVAVSMLSTSPCASILGLCLCSQHRCVLSTAEIRTFTIPPAASGAPLCSGHLTLLGPPHHCTHHTPN
SPAPPPGRGSVPESYDLGTPSPSLGWLLLLPGLVLGSTTYESARLSAVSTCVSVSGGGGGEVS

The following DNA sequence nGPCR-2072 <SEQ ID NO.42> was identified in *H. sapiens*:
AATAAAATGGCAAACTTTTTTCCTAGTAGTTTAAAGGAGTAAACTTGGTTACCCAATAAGATAACTGTAAG
AAAATATTCTCCAGTAGCGAAACATAAACGCAGCAATTGCAAATGTCCACATATAGTATAGATGAGTACCG
TATAGTATTTCCTCTCTTAGAATGTAAGCTCAGGTCAACCAATCCCATCCTCTCTTTATTTCCTCCAGTGC
ATCAAGAAAAACAATGTATAAATATCAGATGCTGAATAAATACTACTGACAAAAGTACCTTTTTTGAAATA
AAGAGAAATTCTACAAAGAGAGTTTATTTTTGAGAGTTTTCCCACACAAACTTCTGGATCAGCATACCAAT
AAAAAACAGCACTGCATCTTGGAATACTCAGGCAAAACTGAGTATATGGGAATCTTAAAGTGCTTCATTCA
TCTTCTGAAATAGGAAATAAGCAGACATTTGTTTCACTGCTTAAGATTTCCTAAATTTTTTCTAAGGTAAT
AGTTTAGAAAGTACCACTTTGTTTCTCCCAACTTTTAGTTCCCTTATTAGACCAACCCGAGGAATAATTTT
TCTACTTTAAAAGTTTTTTCAAGTCAACATCCCTGGGATCTAAAACTTAGT

The following amino acid sequence <SEQ ID NO.152> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.42:
TKFIPGMLTKNFSRKIIPRVGLIRELKVGRNKVVLSKLLPKKFRKSAVKQMSAYFLFQKMNEALDSHILSF
AVFQDAVLFFIGMLIQKFVWENSQKTLFVEFLFISKKVLLSVVFIQHLIFIHCFSCTGGNKERMGLVDLSL
HSKRGNTIRYSSILYVDICNCCVYVSLLENIFLQLSYWVTKFTPLNYEKSLPFY

The following DNA sequence nGPCR-2073 <SEQ ID NO.43> was identified in *H. sapiens*:
CCACAACTTAATAGTTAGAGTGTTCAGAATATAATTCAAAATTTCTTGACATATAAAAAAATGGAAGACAT
TTCAATCAAAAACAAAATCAAACAAGATCAGTCCCAAGATGAAAGAGATCTTGGAACTAGCAGGCAATGAT
TTTAAAAACAGCTCCTATAATTATTCTAAAGAAAGTAAAACAAAATATGCCCGTGATGAGTAAAGAGATAT
AAAATCTTATCAGACACAGAAAGTAAAATGAACAAAATGGCAATTTTATAACTGAAATATACATTATTGGA
ACTAAAAGTTTCAGAGAGTAGACTTAATGACACAAATCCAGAAGAAAGAGATAACAGAGGAAAGAATAAGT
AAACTTAATATCAGTTAATAAGGATTATCCATTATACATTAGAGGGAAAAGATGTGGTGAAAACAGAACAG
AGACTCAGGACCAGTTAAATATCAAATGGTATAACAGATATATAATT

The following amino acid sequence <SEQ ID NO.153> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.43:
IIYLLYHLIFNWSVSVLFSPHLFPLMYNGSLLTDIKFTYSFLCYLFLLDLCHVYSLKLLVPIMYISVIKLP
FCSFYFLCLIRFYISLLITGIFCFTFFRIIIGAVFKIIACFQDLFHLGTDLVFCFLKCLPFFYMS
RNFELYSEHSNYVV

The following DNA sequence nGPCR-2074 <SEQ ID NO.44> was identified in *H. sapiens*:
CATTGTATACCTATCCTTGCACAGACTGTCTTCTGGTCTCCCATTTATCATCCATTTTCAGTTGTCTTGGT
CTTAGTGTTTGCTATCTGTTGGGCCCCGTTCCACATTGACCGACTCTTCTTCAGCTTTGTGGAGGAGTGGA



BNSDOCID <WO 0162924A2 I >

GTGAATCCCTGGCTGCTGTGTTCAACCTCGTCCATGTGGTGTCAGGTAAAACCTTAGCTGGATTTGGTGCA
TGACTAGTATTCAGGTAACAGCACCTTCTTCTTCATCTTGCTTAGATGCCTAAGTACTCCAATTTATCACG
GGGATCTGCCATGCTATAATGAAGACATTTGATTTTTCTTTTATTCAGAGATTGATTATGTTTGATACTGT
TCCAAATACATATATACCAGATCACTATTTCAAGGCTACTTTATGGAAAACCTCAAGTCTAACTGTGATG
ATTACAGAAGGAAAATGGTCAAGGAGTGATTCCTTTGGTTATCCTCCAAATGGCCATGCAATTAAATTGGT
TCTTATTTAGTAAACACCCATGTCCCTGGAAATCTCATATTGCCTTTGGGAAGTATTATATCCTCATGAAG
GAAAACTAAATGGTATTCAT

The following amino acid sequence <SEQ ID NO.154> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.44:
HCIPILAQTVFWSPIYHPFSVVLVLVFAICWAPFHIDRLFFSFVEEWSESLAAVFNLVHVVSGKTLAGFGA
LVFRQHLLLHLAMPKYSNLSRGSAMLRHLIFLLFRDLCLILFQIHIYQITIFKATLWKTSSLTVMITEGKW
SRSDSFGYPPNGHAIKLVLITPMSLEISYCLWEVLYPHEGKLNGIH

The following DNA sequence nGPCR-2075 <SEQ ID NO.45> was identified in *H. sapiens*:
CTGGAAGTGGGCCTTTGGGCAGCTTCCTTTATCCTGGCATTGCCTGTCTGGGTCTACTCGAAGGTCATCAA
ATTTAAAGACGGTGTTGAGAGTTGTGCTTTTGATTTGACATCCCCTGACGATGTACTCTGGTAAGTTGTGA
AAACTTAAGAAAAACGAGTTGAATTAAGTTGTGAAGAACTTCATTCTCCTTGTCAACATGTGAGCAGCCTC
AAAGAGTATCCTTATGGATCCTCTTCTCGCCAGTATCTCCATTAGGTTTCTCCACACATACAATCAAGGTG
ATAAGTTTGATTTTTAAGGAGAGGGTAACCTTTAGAAAAAGATTTTGAATTCAATCATGTAACCTCAGTGG
ACACAAATATATTTAAACATGGATTTTAAACATTCATAGCAGCCAGACGCAGTGGGAATGCAGCAATCAAG
GGAGGTAAGGAATTTCCAGAGTCACTCAGACTCCACCTCATCAGTATGCAATTGCAGTTTGCTTGAATTAT
GTCCCCTATAAAGACATGTTCAAGTCCTACACCAGCTCCCCATACCTGTGAATGTGATCTTATTTGGAAAT
AGGGTTTTTTCAGATGTAATCAAGCTAAGTTAAGGGCATGCTGGA

The following amino acid sequence <SEQ ID NO.155> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.45:
LEVGLWAASFILALPVWVYSKVIKFKDGVESCAFDLTSPDDVLWVVKTEKRVELSCEELHSPCQHVSSLKE
YPYGSSSRQYLHVSPHIQSRVFLRRGPLEKDFEFNHVTSVDTNIFKHGFTFIAARRSGNAAIKGGKEFPES
LRLHLISMQLQFAIMSPIKTCSSPTPAPHTCECDLIWKGFFRCNQAKLRACW

The following DNA sequence nGPCR-2076 <SEQ ID NO.46> was identified in *H. sapiens*:
CTCCTTGGTTTATATATATTTCTGAGTCTTGTTTGTTGACTAGAATGGACTCTATTTCAGAGCTTCTGCTT
TTTGTTTCTGTGTCACCTTGTCATTTTCTAAATTGATTGGGGCACCCTTGGGGGAAGTGGTCTGTGAAGGA
CAAGTGTGCACCAAGGTACTCTGTAGGCAGGGCAGGAAAGGAGTGAGCCTTGGGGGCGAGCACAAGTCAAA
CACAAGCTGGGTTCTTCCTGTCCTCACCTTCCTGGAGAAATCAGGACACTTTGCTGCGGGAAAGCATGACC
TGTTTTAACCCTTTGTGGTGGGGGTGTTTGTTGCAATACTGCTGTGGGAAGGCACCACCCTTTCTTGTTT
TCCACATAGGACTCATATATTCATATTTTTTATACTTATTCTGCCCTCTAATCTCTTTCTGCAGCCATCTC
ATTCATTTTCATCCCAACTACCATTCCGTTTTGTACACTTATAGCTATATTATTGCCTCTTTATCTCACAA
GTTGTGGTATGATAAATAAGTGATGTTTGTACACTGTTTTTGCAAAAAAGCTCACAGTGCTTTCTGGGGGT
ATCTACTAATTAATCTTTACAGAATCCCTATGAGATAGATAGGGCTGGATAGGGTATTCAGCACACAATTC
ACTAGACCATGCTGTCTCTCTATTATGATAAAGGATTATTATTATGTTAAAATGTTTATACACTGAATACA
TAAATTTGTAGAGATTGA

The following amino acid sequence <SEQ ID NO.156> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.46:
LLGLYIFLSLVCLEWTLFQSFCFLFLCHLVIFIDWGTLGGSGLRTSVHQGTLAGQERSEPWGRAQVKHKLG
SSCPHLPGEIRTLCCGKAPVLTLCGGGVLLQYCCGKAPPFLVFHIGLIYSYFLYLFCPLISFCSHLIHFHP
NYHSVLYTYSYIIASLSHKLWYDKVMFVHCFCKKAHSAFWGYLLINLYRIPMRIGLDRVFSTQFTRPCCLS
IMIKDYYYVKMFIHIHKFVEI

The following DNA sequence nGPCR-2077 <SEQ ID NO.47> was identified in *H. sapiens*:
CCTCTTTAAAATTATCAGTGTTCACAGTATCTTCCAAAAGACATGTAAATGTATAAAGGTATAAAAAATAT
ACATATAAATTTTACAATTTTGTGAGCTATATAGTAGATCTCTTATTTTGTCCATAGGTCTTAAAGATCTT
ATACTGTATTCAGGAATAAAGATAACTTCAGTGGGAGGCCTTTACAGGGCTAATGAGTAAGCATTATTTTG
ATAAAGTTCTGTGTTGTCTACAATAGATATAGTAGAAATACTCTTGGAATGGTAATCATCCCAGGCCCTGC
TTTGGAGCGGAAGAAATAGTCAATGTAGAACTTTACAGTATATTGTACACAGATGTGCCTGCTAATAACTT
CTGTAGACAGCAAAGTTTAAGAGAAATTAGGTGGTAAATGCAACATATGTATCTAAATAAATTTGGTCTGA
GGGATTTGATAAGATGAAACAGTACATAGTCCAGAAAATTTTTATACTCAAAGAATTATAGAAAATATCTG
AAATGTTTTCAGTTTTGTGCATATCCAGAAAATGTCATCCTGTGATCTGCTGGTTGGCAGCCCAGTGGCAG
TATTAGATGT



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The following amino acid sequence <SEQ ID NO.157> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.47:
HLILPLGCQPADHRMTFSGYAQNKHFRYFLFFEYKNFLDYVLFHLIKSLRPNLFRYICCIYHLISLKLCCL
QKLIAGTSVYNILSSTLTISSAPKQGLGLPFQEYFYYIYCRQHRTLSKCLLISPVKASHSYLYS
IQYKIFKTYCQNKRSTILTKLNLYVYFLYLYTFTCLLEDTVNTDNFKE

The following DNA sequence nGPCR-2078 <SEQ ID NO.48> was identified in *H. sapiens*:
TAAAAATAATACAATAAAATGCTTGCCAGATAATTCTAACATCTCTGCCATGTTGGTGTTTTTGGTCTATT
GATTGCTTTTTCTCATTTAAGTTGATTCTTAGCATAATGAGTGATTTCTAATTACATAATACTTTGGGTAT
TATGTTCTAAAACTCTGGATCTTATTTAAATCCTTTGTTTTATGTGGACTTTTCTGATACTACTCTAATAG
GAGTGGGGTGGGGTCACTGTGTCATGACTGCCACGTAGGGGTGGAAGTACAGTTTCCCCACTTGACCT
GTATTGATCCTGGAGTGGGAGTGATCCTCACTACAACTCGGTGGGATAGGAGCTACTGCCCCTTGTTGGGT
CCCCACATATACCACCCTGGCTGGGAGTGGCAGGAGTGCTTTGTCATTGTGCCCCATGTGGCCTCCGCTCA
CACTGTGGGGAGGAGTATCCTTGCTGCCCCTGAGTGGTGGTGA

The following amino acid sequence <SEQ ID NO.158> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.48:
KIIQNACQIILTSLPCWCFWSIDCFFSFKLILSIMSDFLHNTLGIMFNSGSYLNPLFYVDFSDTTLIGVGV
GVTVSLPRRGWKYSFPTPVLILEWESSLQLGGIGATAPCWVPTYTTLAGSGRSALSLCPMWPPLTLWGGVS
LLPLSGG

The following DNA sequence nGPCR-2079 <SEQ ID NO.49> was identified in *H. sapiens*:
AGGATCAGCTTGGACATGCCCATTACAAAGCAAATAAGTACATGACATGTCATAAAGCCTCATGAAATTGG
TCACATGCCAAGCACTTCTCCCAGTACTCACAGACCTGGCTAACTGCATACAAAGAAAGGGCCAGGGCCCA
CCTCACCATGGCAGAGGTGTGCTCTGGGCGGTGGCAGCACCAGGTGGGACAGAGGGCACAGAGAAAGCTCT
CAATACTCATGGCCACCAGGAGACAGAGACCCACTGTGTCGGAGAAATAGGAGACAGGATCCAGAAACACA
GCCACCTGCAATGCCGCCTGGTGATACAGCATGAGGATTTTCTCCAGCAGGATCACAGTTACACAGGAGAG
GTTGACCATATCAACAGTGGCCAGGTTAAGGATGTAGGTCACATAGGGGCTGCTCCAGACCTGTGAGTAGA
GAAGCCAGCAGATCACATCATTGCCTACCAGTCCACAGAGGGCCACCAGCACTGTCAGGGAGAAGACCACC
TGCCTGTCCACCAACCACTCACCTCCCGTATGGCTCATGTTCACATGTCCTGAGGTCTCAGTCTCATTGTC
CCAATCCAGCTTTCCAGAGAGGGTTGCGAGAAGCTAGGCTATGGTGGGCTACCTTTTGCTGCCTGCGCA

The following amino acid sequence <SEQ ID NO.159> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.49:
CAGSKRPTIALLATLSGKLDWDNETETSGHVNMSHTGGEWLVDRQVVFSLTVLVALCGLVGNDVICWLLYS
QVWSSPYVTYILNLATVDMVNLSCVTVILLEKILMLYHQAALQVAVFLDPVSYFSDTVGLCLLVAMSIESF
LCALCPTWCCHRPEHTSAMVRWALALSLYAVSQVCEYWEKCLACDQFHEALHVMYLFALWACPSS

The following DNA sequence nGPCR-2080 <SEQ ID NO.50> was identified in *H. sapiens*:
CATTTGAAATATTTCTTTTTTTAAAAATTGATAAAATAATGTAATAGTATACCATTTTGATAATATATAAT
TTATATTAAATTTCAACAAAAAAGCCTGTTTGTAACTAATATTTTTAATTAATTATTTGGTCTTTAAATAT
CTGTCATATTTAAAAACTGATATCTAATCCATCTAAACAAAATCCACTTCAAATTCAAAATAACCTGGAAG
AAAAGCAAACAAAATAACCAACTTTAAGTTGTAAAGATGATAACTATTATCAGGGATGTGCCTGTGTCTGC
TTCTATTTACTGTCACATTTTAGGCATTCTTTTCTACTTGACAGTTCACTTCTGAGTGACTAGGAATGAAG
CTTATTTTAGCCTACTTTTTCCCATTTGTTTTTGTAAAAGAAGAAACACAGAGTATTCTTGAAAATCCAGT
GTGGAACATTTTGATGTTTACCATCAGCAATATTATGAAATATGTCACATATCATCTACATCTTTTTGGTA
ATTATTTATGTACCTTTCATTTTGACACTCAAAAATGGCCACTTTTTTTTCTGTGTATGAAACCCATCTAT
TACATCCGATTTTATTCTATTTCAAAACTATTCCAATCATCATTCATTGGACAAACAGATTCTCAATATT

The following amino acid sequence <SEQ ID NO.160> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.50:
INISFFKNNNVIVYHFDNIFILNFNKKACLLIFLINYLVFKYLSYLKTDISITKSTSNSKPGRKANKITNF
KLRLLSGMCLCLLLFTVTFAFFSTQFTSELGMKLILAYFFPFVFVKEETQSILENPVWNILMFTISNIMKY
VTYHLHLFGNYLCTFHFDTQKWPLFFLCMKPIYYIRFYSISKLFQSSFIGQTDSQY

The following DNA sequence nGPCR-2081 <SEQ ID NO.51> was identified in *H. sapiens*:
GCAAAATGGTAAGGCTATTTATCACAGCACTATCTATAATAGCAAAGTCTAAAAGGATAAAAATGTCCATC
CAGTGTTGGAAGCTGAATAATCTGTTTTACATTTACACAATGAAGAATATACACTGCTTTGGAAGTGATCA
CCAGGATAAATGAACAAAACAAGGTAGAAAAGGATATATGTAATAATATATAATCCTTTAAGGAATGGGGA



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GGGGCAAATGTAATTATATTTGCTTATATTTTTAAAATGGAAAGTTTAACCTAAAACTAATAAAAATGACT
TTACTAGTTTAACTGACTCAACCATTG

The following amino acid sequence <SEQ ID NO.161> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.51:
MVESVKLVKSFLLVLGTFHFKNISKYNYICPSPFLKGLYIITYILFYLVLFIYPGDHFQSSVYSSLCKCKT
DYSASNTGWTFLSFTLLLIVLIALPFC

The following DNA sequence nGPCR-2082 <SEQ ID NO.52> was identified in *H. sapiens*:
CTCCTGGGCCCGGAAGACGGAAGACTCGGTGGCGCCTAATAAGGAGTAGAGGAGTCGGTTTACCAGGTGTG
GGATGAGAGAACTGCCCCGACGCCCCCTTTCCCCACCCCAGGCAAGGAAGTCCAGCTGGTTGGGCTGGCTT
AGCCTCTCCCTCCCGTGAAATGGAAAACTCTCTCTATGCGGAGTTCTGGGGACTGACTTGCCTAGAGACCC
CTCCTGGCCCAGACTAGTCCCCACTCCCCTCCTACTGAGCTTCTGAGCGTCCGACGAGGCACAGTCCCTCC
CGTCGTGCAGCGGGAAAACGGACTCCCCGAGAGGTTGAGGAATTTGCTCAGAGTTACACAGTGGGGAAGAC
GCCAAGCCAGGATTTTAACGCAAGTTGTCCAGACTCCAAGGGCCAGATTCTCCTCTGACATTAACGCCGTG
CCCCAGGACCATGGACTGCTTTCCCTAACACCCAGACAGAAAACTGCGATGCCTTGGGTATGATTGAAAGA
CCCAGATAGGGATCCCCCTTCCCAAGTGGGTTGGGCGGATGCGGCCGCTGTCCCCGCGGGCGGTGAGCGAC
GC

The following amino acid sequence <SEQ ID NO.162> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.52:
RRSPPAGTAAASAQPTWEGGSLSGSFNHTQGIAVFCLGVRESSPWSWGTALMSEENLALGVWTTCVKILAW
RLPHCVTLSKFLNLSGSPFSRCTTGGTVPRRTLRSSVGGEWGLVWARRGLASQSPELRIERVFHFTGGRGA
SPTSWTSLPGVGKGGVGAVLSSHTWTDSSTPYAPPSLPSSGPR

The following DNA sequence nGPCR-2083 <SEQ ID NO.53> was identified in *H. sapiens*:
GCCATCCCCAGGAAGCTTTTAGAGGACAAAAACTTAGTTTCTGCATTCATTGCTCTGTGTAATTAAAATTG
GGAGTAATCCCCCTACACACAGTATGAAGGGGAATACAGTAGTGAAAAACCTCAAATTTTTCTCTGTAAAT
TGAAGTAATTGACCTGGGTGGCATCTAAATTTCGAACGCTCAAAAAGGTGAGTTGACCTTGCTGTCTATCA
ATTACCCACTGTACTCTCAGATCCTTGGAAATTTCTCCATATCCTCTGGAGGCCTTTCAGAGCAGAAATTT
GCTTGGGGGTTTGTGGGACTGAGCACTCAGGCTAGTGTAGAATGTGGCAGAGCATCAGATCACTGCTCTGA
AGACCATCCCTGTCATAGCTCTGGGGTTCTTTTTTGGAAGTGGAACCAGAGTCATTTTCCAGGCTGGGATG
ATGAACTTGTGAGTTAACTGGATACCTCAGAACAGTGGAGGCAAACAAGGAAGCACAGGAGGCTTCTGAGG
TCTCTTACATTGCCCTGGAGCCTGTAGGCCTCACTCATTTGCCCTCTTGTATCATAGTTTATTTGTTTGTT
AAATTATTTTTACGTTTGGATTTAAAATTTTT

The following amino acid sequence <SEQ ID NO.163> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.53:
PSPGSFRTKTFLHSLLCVIKIGSNPPTHSMKGNTVVKNLKFFSVNSNPGWHLNFERSKRVDLAVYQLPTVL
SDPWKFLHILWRPFRAEICLGVCGTEHSGCRMWQSIRSLLRPSLSLWGSFLEVEPESFSRLGTCELTGYLR
TVEANKEAQEASEVSYIALEPVGLTHLPSCIIVYLFVKLFLRLDLKF

The following DNA sequence nGPCR-2084 <SEQ ID NO.54> was identified in *H. sapiens*:
AATAGTCCAGACTAAAAATTTGATTAATTTCCAAGGTAAGAAATATACAGTTAATTCCTGCTAACACTAAC
ACAGAAAAAGTGAATAAAGATTATCAAAAACTTTTTAATAAAAGAAGCATTTCTGTAGTTAAAGTGATTA
AGAAGAAATCAGGTAAATGAGAACAAACTTTATGAATCAGGAGAAAAATAATCATTTGTAAAAAAAAATCC
TCAAATGCAGTCATCTTATGCTAAACTCTGCTCATATTTTTTTCAATAAACAAGCAATATTATATGCAAAT
TATTATGTAGTTAACATTTTTGGAAATTTAATTATAATGAAAAGAGTTTGGAGTTTTTTTGAAAGACATAA
ATTGAGTCTTTATTCAGATACCAACTACATGATTGTAGGCATGACATATGTTCTAGATCACGGATTTTCAT
CTGTAAATTGGGGAAGCTAATTTCTTTTTAAGATTATGTCCCAGTACATTATTGCATATTGTATATACTTT
GCATTATTGCCTAATTCCTTGTGCCTGAGTTTATTGTATAAATTACTGAGGGCCAAAATGAAGTTGTAAAC
CAACATTGAAAAAAGAAGCACACTAAAATCAAATAGTAAGCTGAAAAATAACTAGTTTAAATTTCATCCAG
ATGTATCTGCTCATATGTCATTCAAAATCTTCGGCCAATTATTATTTACATTTAAAAAATGCAAATGATAT
CTGCTAGTAC

The following amino acid sequence <SEQ ID NO.164> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.54:
VLADIICIFMIIIGRRFMTYEQIHLDEITSYFSAYYLILVCFFFQCWFTTSFWPSVIYTINSGTRNA
IMQSIYNMQCTGTSKEISFPNLQMKIRDLEHMSCLQSCSWYLNKDSIYVFQKNSKLFSLLNFQKCLHNNLH
IILLVYKKYEQSLADDCIGFFFTNDYFSPDSSLFSFTSFLLNHFNYRNASFIKKVFDNLYSLFLCCQELTV
YFLPWKLIKFLVWTI



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The following DNA sequence nGPCR-2085 <SEQ ID NO.55> was identified in *H. sapiens*:
CAACATATGTTCCCAAATTTATTCATAATAATGAATGTAACTAGATCAATTTCTTGATGTACAGTATTAGT
CCATCAGATAACTATGCTATATTTATCCATCTTTTATCAGTGTGTATTTCAGCTGTTTCCCATTTGAGGTA
AAGGGGTATACAAACAATACTGCTATGAACACTCTTCAGCATGACTGCAAATATTCATGACCAAGAATTTC
TCCCAAGCAGTGTTTTTCAAACTGCAGACTGCAATCTAGTAATGGGTCATTAAATCGATTTAGTTACAATA
AGTGGCATTTTTTTAAACGGATTATAATACAATAGAAAATATCAAGGTAATAGGCACACATTCTTAGCAAT
GAAACTACAGTTAAAGGAATAAACTTATAAAACAGACATGCTTCATAAATTATTTTCTAAATTTTTATCAT
GTTTAAGATTTTTATTGTATTTAAATATTAGTAAATTCACATTTGATATAAACATTTTCATATATTTACCT
TAATTATATGTAGTAAAAATAACTTATACGAAACTTACTTCATGTGTGTATAATGGGTCATGAAGTAAAAT
GTACTTCAGCGTGGGGGATCATACTAACAAAAGTTTGAAGAACACTTCTCT

The following amino acid sequence <SEQ ID NO.165> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.55:
EKCSSNFCYDPPRSTFYFMTHYTHMKVSYKLFLLHIIKVNIKCLYQMIYYLNTIKILNMIKIKIIYEACLF
YKFIPLTVVSLLRMCAYYLDIFYCIIIRLKKCHLLLNRFNDPLLDCSLQFEKHCLGEILGHEYLQSCRVFI
AVLFVYPFTSNGKQLKYTLIKDGIHSYLMDYCTSRNSSYIHYYEIWEHML

The following DNA sequence nGPCR-2086 <SEQ ID NO.56> was identified in *H. sapiens*:
ATGTAGATTGCACAGTTAGGAAATAAATTGGCCAACATTTACTAGTTAATCTTTATTAAGAACTTACTGAG
TGTCAGGTGCTGTGGTAACACATTATGTGCATTACGTTTGTAAATCCCAACAATGAATTAAGCAGCCTTAT
GATTCTCATCTCACAGAATCTAGAGGTAAGTAACTTGCCCAAGTTACACTGCTGGTAAGAAGCCCTACTTC
ATCAACAACAACTACACTTGAAACAATAGCAAAATTGAAGTGTGACAGTAAACTGAATGCAATATACATTA
CAGTATAATTTATTTTATTACTTACACATTTCAGCAAAGTGCAAGTTTTCTGGAGTATTTATCTTGTTCCC
ATAGATGTTGTACAGGGAATTCAATAATAAGAATAGTAGCCAGAAAAGAAAAAGGCAGAAAACTTAACAGT
TATAAGAAAATGAAAAATTTTAGTACTTTTTTCTATTCCCATGCTATATATCATAATATAGAGGAAATTAA
AGAAAAATATTTTTGATTACATAACTTTTAAAAATAATAATTCTGTAGGTGTGAATATGTGTGTGTTAACC
TGTATGAGTGATTAATATGTCATTAGAAGAAAGGATGTTACCCACTCTAAAATAATGTTAGATGACATTTA
TGCACTAATAATATGAACCA

The following amino acid sequence <SEQ ID NO.166> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.56:
MIAQLGNKLANIYLIFIKNLLSVRCCGNTLCALRLIPTMNAALFSSHRIRVTCPSYTAGKKPYFINNNYTN
NSKIEVQTECNIHYSIIYFITYTFQQSASFLEYLSCSHRCCTGNSIIRIVARKEKGRKLNSYKKMKNFSTF
FYSHAIYHNIEEIKEKYFLHNFKFCRCEYVCVNLYELICHKKGCYPLNNVRHLCTNNMN

The following DNA sequence nGPCR-2087 <SEQ ID NO.57> was identified in *H. sapiens*:
ATAGTCTAGTGGGGAGGACCCAGCCACCGAATAAGAAAGCCAATTCATCAATCCCATCATTGCAAGTGTTG
GTAAGTGGCAAGAGGGACAACAGTATAATGGTATGATCACAAGGACTAGAATTGGTGGGGGAGAGCTAGTT
TATATTTCATGGCCAGCAAAGGCTTCTTTGAGCAGAGGAATTTTTATCTGAGTCCAAACAGGGGGGGCACA
ACCATGCAAAGATGGGCATTCAAAATAGAGAAATTAGCAAACACAAAAGCCAAGGGTCTGTCCTAAGAAGG
AAAGGGAAGTTGGGGTGAAGAAAAGAGAATCAAAAGTGTGCAGGCAGGACCTCATGGTCCAGAAGAAGTCT
GAATTTCATTCTCAAGAGACTCGGAGGCCTCTATAGAATTTGAGCATGGCTGTGTAGCATTTTTTTCTTTT
TTCTTTTAATTTTTAATTTTTTTTATTTGAATACAGACATCATTTCAAGAGACTGAATAGCATTTTCTAAA
GGCTACTCTGACCACTGGTTGTGGAATGACTGTGAAGGGCTGTGGGGAAGGGGGAATGGGTGCTCCCACAC
CTTCACACTCAGCCTGTTTGGCATTTGCTTTCATTTTGCTCAAGTGCCACAGGGCTTAGATTAGAGTGATC
T

The following amino acid sequence <SEQ ID NO.167> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.57:
DHSNLSPVALEQNESKCQTGVRCGSTHSPFPTALHSHSTTSGQSSLKMLFSLLKCLYSNKKNKLKEKRKKC
YTAMLKFYRGLRVSENSDFFWTMRSCLHTFDSLFFTPTSLSFLGQTLGFCVCFLYFECPSLHGCAPPVWTQ
IKIPLLKEAFAGHEITSSPPPILVLVIIPLYCCPSCHLPTLAMMGLMNWLSYSVAGSSPLDY

The following DNA sequence nGPCR-2088 <SEQ ID NO.58> was identified in *H. sapiens*:
TTGCAGGGTAGTGATACACATCTTTATTCGAATTCTGAGTATTTAACTGGTTATTTTTCATGCTAACCTAC
ATTAGACAGTTCTCATGTTCAAAACATCCAGTCTATTTAAGATTGGATTCCCCAAGAAAATGTGCTACACA
TGTGAAAATGAGTACAGGTTGAGCATCCCAAATCCAAAAATCCAAAAATACAAAATCTGAAATGCTCCAAA
ATCCAAAAGTCTTTGAGTGTCAATGTGATACTCATAGGATATGCTCAATGGAGCATTTTGGATTTCAGATT
TCCAGATTTGGGATACTCGATAAGTGTAATGTAAATATTCCCAAATCAAAACATATCTGAAACCTGAAACA



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CTTCTATTCCCAAGCATTTCAGATAAGGAATACTCAACCTGTAATTTAAATCAATGCCAGAAGAACTATTA
GGGGAAAATAAAATTTAATAACCAAAGTTAGATTTTACAGCTTTAATGGCAACTTTAGAACATTTTAATAG
CACAAAAGAATAAAACAGACTTTATAATATCATAGCAAGTACAAAGCAAAATAGTAACTTTATTCTATGAA
TTAAAAAGTCACAGTATGACATAGTTCTTAGGTTTACAGCCACTATACAAGGGACAAAGCCAGAGCCAA

The following amino acid sequence <SEQ ID NO.168> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.58:
GSGFVPCIVAVNLRTMSYCDFLIHRIKLLFCFLLAMILSLFYSFVLLKCSKVAIKAVKSNFGYILFSPNSS
SGIDLNYRLSIPYLKCLGIEVFQVSDMFFGNIYITLIEYPKSGNLKSKMLHAYPMSITLTLKDFWILEHFR
FCIFGFLDLGCSTCTHFHMCSTFSWGIQSIDWMFTELSNVGHEKPVKYSEFERCVSLPC

The following DNA sequence nGPCR-2089 <SEQ ID NO.59> was identified in *H. sapiens*:
AATGGATAATGAAACTGAGGCATATCCACATACAAATTATTCGGCCTTAAAAAAAAAGAATTTCTGCCATT
TGTAACAACACTGAAGAACTTGGAGGACATTATGTGGAATGAAACAAACCAGATACACACAAAAAACACTG
CAGGATCTCACCTGTAAGTTAAATCTAAAGTTGAGTTCATAGATGCAGAGAGTAGAATGGCAGTTATCAGG
GATGGGAAAATGGGGAGATGCTGGTCAAAGGATAGAAAGCTTCAGCTGTGCAGGATGAATACATTCTACAA
ATCTCGGGTACAGCGGTGGCCTACAGTTAACAATGCTGTACTGTATATGTAATATTCCCTAAGGGAGTAGA
TCTTAAGTGCTTTGTCACAAAAAAAGAAGAGGTAACTGTGTGAAGAGAGGGATGTGTTAGTCAGCTAATTC
ACATATAGTCACGCTAGATGATAACAATCAGCTCACTATATATATCAAAACGTCACACCACATACCTTCAG
TACGCAATTGTAATTTCAAAAAATTATGGCAAACATTGTAAGAGTTTAGTCAAATTATAAAATAATTACAT
ATCTACTCTGTGACCAGACTGTGTTTGATAGGGAGATGATGTTTCTAAAATGGAAAGCTATCTAGTCACAT
A

The following amino acid sequence <SEQ ID NO.169> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.59:
MLDSFPFKHHLPIKHSLVTEICNYFIILNSYNVCHNFLKLQLRTEGMWCDVLIYIVSLLSSSVTICELADH
IPLFTQLPLLFLQSTDLLPGILHIQYSIVNCRPPLYPRFVECIHPAQLKLSILPASPHFPIPDNCHSTLCI
YELNFRFNLQVRSCSVFCVYLVCFIPHNVLQVLQCCYKWQKFFFFKAEFVCGYASVSLSI

The following DNA sequence nGPCR-2090 <SEQ ID NO.60> was identified in *H. sapiens*:
TTCATTTAGTGACTGTCTCTCCTGCTAGTGGCTCAGCTCCACAGGGGCAGGTGCTTTGTCATCTTATTTCG
TGTGGTATCCCTGTATCTAGGATGCGGTGCTGGTACTGAACAGGTGCACAGTCAGTAGTTAAGGAACAATT
GAATGATGACTGCTGTTCTGGGCTTATGAGCTTTTTCCTGTGCCTTATTGTCATCCAATATTTGCTATTTA
TAAGATGTCAATTTTTTTTTAAATGTAAGGGGTTGATGAGCTGTTATTTGGTTTTATTGAGGGGTGTTTTG
GGACATTTATCTCAGCAAACCATGGCCACGCCTCCATATAATGTCCAAGAGAAAGAGCCTCTAAATGCAAT
GTGTTGGATGTTAGCTAAGTGAAATCACCACAAGAAGCTCATGACTCAAATCACAGAGGCTCACAAGGCCC
TAGTAGAACGGGCACCTCTGGGCTTGCCTGTGGGTTTTCTTGGTATGTCTGTATCGCTGT

The following amino acid sequence <SEQ ID NO.170> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.60:
SFSDCLSCWLSSTGAGALSSYFVWYPCIDAVLVLNRCTVSSGTIELLFWAYELFPVPYCHPIFAIYKMSIF
FMGVDELLFGFIEGCFGTFISANHGHASICPRERASKCNVLDVSVKSPQEAHDSNHRGSQGPSRTGTSGLA
CGFSWYVCIA

The following DNA sequence nGPCR-2091 <SEQ ID NO.61> was identified in *H. sapiens*:
AGCTCTGTCCAGAGGGCTCACTAAAAAAACTTGGGTTTCTATTAAACTAGTTTCAGACCACTGTGTTTTGC
TCTGTTGAAGCATAAACTTCAATAAAATTAACAGTAAGTAAACAGCAGCTATGAAGCTATCGGGAGGTTCG
CTTCAGGGTTTGTTTTCCTTTAACATTTGCTTTAATTCAAACCATAAAGGAAAATATTATACCGTAGCAAG
ACTTAGCAATACTTTAGATAAACAGGGCCTAAACAGATATAGATAATATAGATAATTATTTTTCTCAAATA
TATATTTCATATTATATATAATTTTATAGAACTGTATCAAAATGATTACATAAGTATTATATATAAAAAAA
CTATTTTTCCCAAAATGACAATAAGCATTACCACAGCGCAAAATCTGTGCCACAGGAAAAACTATCAGAAA
GACCCCTTTACCTTCCCTTAACCATTAATACAGAACAAACACAACACCAGCGAGTCCCTGCTTGTGTGGAG
TGCCTCCTAAGAGAAATAAGTATTAGTAAGACAGCTGTTTCTGGATAATGGGCTCCTGTGTCTGTGAAAAC
TGCTACAAACCAAACAGTTTAGATTTTTTGACCTGACCT

The following amino acid sequence <SEQ ID NO.171> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.61:
GQVKKSKLFGLQFSQTQEPIIQKQLSYYLFLLGGTPHKQGLAGVVFVLYWLREGKGVFLIVFPVAQILRCG
NAYCHFGKNSFFIYNTYVIILIQFYKIIYNMKYIFEKNNYLYYLYLFRPCLSKVLLSLATVYFPLWFELKQ
MLKENKPSEPPDSFIAAVYLLLILLKFMLQQSKTQWSETSLIETQVFLVSPLDRA



BNSDOCID <WO__0162924A2_I_>

The following DNA sequence nGPCR-2092 <SEQ ID NO.62> was identified in *H. sapiens*:
AAAAGCAAAATCTTGAGTCAGTTGAAGCCATGATATTTTATTCCTTCATGACCTTGAGATAGCAGTGCTAA
AACCATGGTTTGTACCTATCATATTTTTTTCTTTATTCAATGATATTATTATACTGGGTAATATTTGGTAG
TCAAGAGAGCATGGCCCTGGTTTGGAACTTCCATGGATGAGTACATAAGAATGATTTTAATCAGCATATAA
TTATATAGAATCATATATATATAGGATCTAGATATAGATCTACTTGCTGACTTGCCCATTCACACATCTCT
GTGTCCCATCAGTCCTCAACAGAAAGAGGATAGCAGATATTCCAGAAGAAGGGACTGGAAAACCATCTAGA
GCAAGTTGCATCTTTGATTTACAACCTAGGAAACAGAATTGGGGAGCCGATCAAAGGATCTTGCTCCTTTG
CCCCAGAAAACAAAACTGGGACACCAGCAATGACTGTTAAATAGTACCATAGGTTGCCTTGCAATTCAGAT
CCTTCCCGCCTCCATCTCTGGGGATCTTTAAGGACCAGGGGATTTGGGA

The following amino acid sequence <SEQ ID NO.172> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.62:
KQNLESVEAMIFYSFMTLRQCNHGLYLSYFFLYSMILLYWVIFGSQESMALVWNFHGVHKNDFNQHIIINH
IYIGSRYRSTCLAHSHISVSHQSSTERGQIFQKKGLENHLEQVASLIYNLGNRIGEPIKGSCSFAPENKTG
TPAMTVKYHRLPCNSDPSRLHLWGSLRTRGFG

The following DNA sequence nGPCR-2093 <SEQ ID NO.63> was identified in *H. sapiens*:
TCCCTTTCTGCACTCTGTTTTATAACTGCAGGGCCTGGAAGCCTGTATACTCCATTTGCCAGAATCCTTTA
CCGACTGGCTTCTAGTCAAATTTGGCCAATGAGAGTTACTGGTGAGAGGAAAGACGCCATTCTGATCTGGC
ACCAGTGGTGGAGGTGTCTCAGTGGCCAATTCGGCACTGGCCACATAGGGCCTCTTCTGTGAAGGTAGAGA
ATGGGCACTGGCCACACCGTAACCTCCAGCAGCAAATGCAGCTAGAGGGCTCCAGCCTAAGAGTGGTAGCA
GCTCTCTCATCTCTGGGCAGCCTTCGTTCCTTTCTCCCCCAGCCTTTCCAATGCCTTTGCAACCGTTTCCC
AGAATTAAATCCCTTTGTGTTTGAATGATGTACAGTGTTTTTTGTTTTCCTGATTGGGACTGACTGGCTGA
TTATAGACCAAAGTATTCAGAAGCTTTGGGAAACCAAGGGGTTTATAAGTCAAAATAGTGTAATGCTTTTC
TGGAAACCAGTCTTCCCTCCAAACTGTTATCAGGCAAATTTTATGCAGTTCTT

The following amino acid sequence <SEQ ID NO.173> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.63:
KNCIKFAQFGGKTGFQKSITLFLINPLVSQSFILWSIISQSVPIRKTKNTVHHSNTKGFNSGKRLQRHWKG
WGRKERRLPRDERAATTLRLEPSSCICCWRLRCGQCPFSTFTEEALCGQCRIGHDTSTTGARSEWRLSSHQ
LSLAKFDKPVGKGFWQMEYTGFQALQLNRVQKG

The following DNA sequence nGPCR-2094 <SEQ ID NO.64> was identified in *H. sapiens*:
TTGAAATAAACTCTTCTTTTTGTTTTCATTGGAAAAGTCTCTTCCCTCTACTCACACTGAAGGCTTGACTC
ATATGAGTTTTTCCCAATGACACCTTTGATAATTATTTGATAAAAATAATACTGTTTAAAAAAAAAAACCT
CGCTTTTATTCTTAACCATAGTTCAGTTTTACTCTGAGATATGATAATGAAGCCTATCAAAGAATGTTCTC
CGGGAGTTAGTTCCGTGAGCTCTGGTTTCCCTGTGGAAGGCCACCTGTGTGCTGCTGCTGTGGGAGAATGT
AGGGCTTGAGTCATCTCTTTCCCCTCAAGCTGCCATCCATTTCTCACCAACTTTTGACCACCTCCCAGAAG
TGAGCTACAGTCATGCAATGTTTTGGTCAAAGACTAACCACTTATACAATGGTGGTCCCATGAGATTATAA
TACTATATTTTTACTGGGTTCTTTCCATGTTTATATATTTAGATACACAGATACTTACCATTGTGTTACAA
TTGCCTACAATATCCAGCAGTAACATGCTGAATAGGTTTGTAGCCTAGGAGCCATAGGCTATTCCCTATAG
CATAGATGTGCAGTAGGCTCTACCATCATG

The following amino acid sequence <SEQ ID NO.174> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.64:
HDGRAYCTSMLGIAYGSATNLFSMLLLDIVGNCNTMVSICVSKYINMERTQKYSIIISWDHHCISGSLTKT
LHDCSSLLGGGQKLVRNGWQLEGKEMTQALHSPTAAAHRWPSTGKPELTELTPGEHSLIGFIIISQSKTEL
WLRIKARFFFLNSIIFIKLSKVSLGKTHMSQAFSVSRGKRLFQKQKEEFIS

The following DNA sequence nGPCR-2095 <SEQ ID NO.65> was identified in *H. sapiens*:
ATCTCGGGGCAGCCCCTAAGATGAATGCTATTGGTTTGCACTTAGCCTTCATTAGACGTTCCTTCCACAGA
TACTTACTGCACACTCATTCCAAGTCTAGGTACTCAGGGTACATCAGTGAACAAAACCCATACATTAGTCC
GGTTCCACTGAGAAGAACATGCCATGATAGGATGACGTTTCCTGGAGAAAGAGCAAGGAAAGACAAGGAGA
GCCTCACACTGTGATGCAGGTCTGATGCCTGCAGAAGGAGACAGGGAAGGGAGGAGGCTTGGAGTAGAACA
GCCTTGGGCTGAAGTGCAATTCCAGGAATGCTCTGGCCCCACCAGCGGGGAATTCTTGAACCAAAGTCACC
CATAAGAGAGTCTTGCATTTTGCCAAATGGATCCGTGTTAATGACCTTGCTGTGCTCAGCTGCTGGCTGGA
AACAGCCCGTGGGAAGTGTGAACTCAATATGAATGTGATGGTGGGTCCCAAGGGGTGAGCTGAGACGGTGA
GTCCATTGTGCTTCTCACAGCAGAGATCTGAGCCTTGCAGTTTTCATGGACACCCCTAATGTTTTCATGGA
GTGAGAGAGACAGAAGGCACTCAGTAAGCATAAGAAATGAATGAATAAATAGATAAAGGTATGATAGAAGC
CTGTAAGTATTATGCAAAACCCGAGGTGGCACGGAGAAGGATTGGGAGTGCCAGGATGGGGAGGGCTGCAA



BNSDOCID <WO 0162924A2 I >

CTGAGG

The following amino acid sequence <SEQ ID NO.175> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.65:
LSCSPPHPGTPNPSPCHLGFCIILTGFYHTFIYLFIHFLCLLSAFCLSHSMKTLGVSMKTARLRSLLEAQW
THRLSSPLGTHHHIHIEFTLPTGCFQPAAEHSKVINTDPFGKMQDSLMGDFGSRIPRWWGQSIPGIALQPK
AVLLQASSLPCLLLQASDLHHSVRLSLSFLALSPGNVILSWHLLLSGTGLMYGFCSLMYPEYLDLEVCSKY
LWKERLMKAKCKPIAFILGAAPR

The following DNA sequence nGPCR-2096 <SEQ ID NO.66> was identified in *H. sapiens*:
CCTGGTTTAATGGTATAAATTTATAATCATAAAAATATTTTTAATAAAAGATTATAAACCTTCTCCTAATG
GCCAACTATTTTTGAATTTCTGCCTTAATATTTTGATGATACTTTTATTTCTTCCTCAAGACACATTACCA
TGTCTATCATGTCTCCTTTCACAGTGCAGCACCATCATATTTCCATTAACATGTGGCTCTGGACATACAAT
AGATCCAACTGCACCCCTTAAAACACAGCGGCAATGTGGTAGAGAAAACTGACTTAACATAGTAAAAACTA
TAGCCTGAGCTCTGCTCACCAAGCTGAGTATTACAGAGACATTATCCTGTTTCCATTTGATAGAGTTAAAG
TGATCTCAATCAGAGAGCAAGATCTAAGCTTAATGGGTAAAAATTCAGAGTTG

The following amino acid sequence <SEQ ID NO.176> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.66:
QLIFTHAILLSDDHFNSIKWKQDNVSVILSLVSRAQAIVFTMLSQFSLPHCRCVLRGAVGSIVCPEPHVNG
NMMVLHCERRHDRHGNVSGRNKSIIKILRQKFKNSWPLGEGLSFIKNIFMIINLYHTR

The following DNA sequence nGPCR-2097 <SEQ ID NO.67> was identified in *H. sapiens*:
TTCTGAAACTAAGCAAAAATGAGCCTTAAATTGTTCAGTTGGTGAGATAGAGCAGAGACTTTGGATGATGT
AGAACATGAAGATGTATGTATATATTCATTTTTGGAGGGGGGTACATTCCTCTCTGGCTACTATATACTCC
TAGACAAAAAAATACAGTCATCAATCACTGATTCAGTTAAATATCTGCTTGGCAACGCGTTTCACAGATAG
GCTATTAGAAGAAACAAGCAAATGTTTACTGAGTACATACTGTGTTCCAGACACAGTGTTAGGAACTGGTG
GATAAAACATAAGGAGAAGGACAAAGACTGTCCAGTGGCAGCTACAGTCAATGGCAGGGAGTATGATCAAG
TAATTGGCTAATGGCATCACTGGGTACCACAGCAGTATAGGGGAGGAATATTCCAAACTGGGGAGGGATGG
GGAGTTTGGTCAGGGAAGATTTACCATAGAAAATGCTAAGATGAAACCTGAAAGGCTAGAAGCAGTTAGCC
AGATTCAAGGGTAGGGAGAAGACTTTTTTAGGCAGATGACACCGCATCCATGGAAGCAAGGGGTGGAGGGA
ACCAGAAG

The following amino acid sequence <SEQ ID NO.177> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.67:
LLVPSTPCFHGCGVICLKKSSPYPIWLTASSLSGFILAFSMVNLPPNSPSLPSLEYSSPILLWYPVMPLAN
YLIILPAIDCSCHWTVFVLLLMFYPPVPNTVSGTQYVLSKHLLVSSNSLSVKRVAKQIFNISDLYFFVEYI
VAREECTPLQKIYTYIFMFYIIQSLCSISPTEQFKAHFCLVSE

The following DNA sequence nGPCR-2098 <SEQ ID NO.68> was identified in *H. sapiens*:
ACCTCCTCAAGACCTCATAGGATTAAGTGAGATGTTGACACACCTCACTGCACTGAGTGGCAAACATTCAT
CCCATCCCTCCTCCCACCAGTGGCCAACCACAGGGCATCTCTGGTTTACATGACCTACGGCAACTCGAGGC
CATTCACAGTAAAGGCCACTCCAGATAGTGATGATGACACTCACTTGCAGAGGCAGGAGGGTCCCCGCACA
CCCCCCTCCAAAGGGGCACACACACAGATGACCAAATGCATCCCATGAGGCAGAGCCACCCAAAGTCCCTT
AGACTAAAAATCGTCTAACACACACACACACTGTTGGAGCCCAGTCCGCGGAGTGGGTGAGTATTTCCCTG
TCCAAATAGGTGGCAGAAAAAAATACCAGGGACTGACTTCTCTCTGGCAAACCAAGACAAACTTGCCATAG
AGCATCTCAGTGGCCAGCAGAGGAGAGAGGAGGTCATTTGGGACCATTTACTCATGCGAGAGTCACTGCCC
CATGCTAAGATTTCCCCTAAAAATAAAATGATAAGATAATAACTCATAATGCTCTCCCCAAATCAGTACCA
CACAGACCCCCCTCTTCTGTTTGCTCAGACCCCCGCTCTCCAGCA

The following amino acid sequence <SEQ ID NO.178> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.68:
AGERGSEQTEEGGLCGTDLGRALVIILSFYFGKSHGAVTLAVNGPKPPLSSAGHDALWQVCLGLPERSQSL
VFFSATYLDREILTHSADWAPTVCVCVRRFLVGTLGGSASWDAFGHLCVCPFGGGCAGTLLPLQVSVIITI
WSGLYCEWPRVAVGHVNQRCPVVGHWWEEGWDECLPLSAVRCVNISLNPMRSGG

The following DNA sequence nGPCR-2099 <SEQ ID NO.69> was identified in *H. sapiens*:
ATAATCCACTGGCCTCTTTCTGTGGGATGCAGGCGTTCATTCTCCCTCAGTGGCTCAGGGAGGCTGAGCAG
AGCCATATAAACCTAGGGAGAAGCCCGTGCTTGAAGCCTCATGTTGTGTCTGTCAAGGAAGTTTCAAGGCT
AGGACCAGCCTCCACGGGGCAGAGAAGTCGTGCTTTCTGCTCTGGTGGGGTGTGATGGCTCAGTTTGTCAT



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GCAGGTGACCCAGGTGACACCAGTCAGGTGGCCTCTTCCTGGCATTGCAGTTAGAATGTGCCTTGAGCCAC
ATGTCAAGGCAATTGAGTGTTTGGAGTCCTCAACGTGCCCCCTTCCAGTCATCCTGCTCCTGAGGATGTGC
TGTTGCCTGGTTCCCAGCCTGCTGCAGCTCCGCGGGCCGCCCCCTCCCTGTTCACCCAGGGGAGCAGGCGT
GTTCCCTCCGCAGGGGCTTGAGACCTGCCGTCCTTTCCCCTGGACCCTCCCTCTCCCCCAAGCCCTAACCC
AATGCCACTCCTTCCTGAGGCTGATGGTGGCTTTGCGTGAGGTGGGCCCTGCTGAGCAGCAGAGAATTTCT
TAGAATTTTCATCGCCAGATGGCTCTGGGTTAGGGCTGA

The following amino acid sequence <SEQ ID NO.179> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.69:
SALTQSHLAMKILRNSLLLSRAHLTQSHHQPQEGVALGGLGEREGPGERTAGLKPLRREHACSPGTGRGRP
AELQQARNQATAHPQEQDDWKGARGLQTLNCLDMWLKAHSNCNARKRPPDWCHLGHLHDKLSHHTPPEQKA
RLLCPVEAGPSLETSLTDTTGFKHGLLPRFIWLCSASLSHGRMNACIPQKEASGL

The following DNA sequence nGPCR-2100 <SEQ ID NO.70> was identified in *H. sapiens*:
ATAAACAAAACGTTGATAGTTTGAACAAATGTTAAAAAGAAAATAAATAGGATATGTGATGGAGAATGATT
GGCAGGGTGCCTATGTTAGATGAGGAAGAGTCAGAGATATAGCCTTTCTGAAAAAGTGACACTTAAGATGA
CAAAAGAAGAAATAAGAAAAGCCACAAGCCCAGCGTCTCAGGAACAGGATTCAGCAAGTCTGAAGCCCCAA
CGCAGAAAAGTGTAATGCGTCTTCTAGGGGCATAGTGAGAAAGGGGGAACAAAATATGACAAAGAGGGTTG
GGCTGGAGACCAAATTGTGGAGCCGTCAGCACAAATATGGCATTTAACATTGCAGGGAAGGAAAAGATGAC
CCAGAGGAAAGGTGTAGATAGATGAGGCAGAAATGAGAAGACCCAGCACACAGAGGAACAGCCTGACTTTG
AAGTCTGGCCAGACTTTAAAGAGGAGGCTGGGAAGGAGGGCAGTGATGGACGAGGAAACAGAAAGTACAAC
CAGACAAATGCCAAGACAAGAGACTGCTTCTAGAATGTAGGAGCAGCCATCAGCTGAATTCAGCTAGTAGG
CTGTGGAAGGTGGTACAGGCACAAACCT

The following amino acid sequence <SEQ ID NO.180> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.70:
GLCLYHLPQPTSIQLMAAPTFKQSLVLAFVWLYFLFPRPSLPSFPASSLKSGQTSKSGCSSVCWVFSFLPH
LSTPFLWVIFSFPAMLNAIFVLTAPQFGLQPNPLCHILFPLSHYAPRRRITLFCVGASDLLNPVPETLGLW
LFLFLLLSSVSLFQKGYISDSSSSNIGTLPIILHHISYLFSFHLFKLSTFCL

The following DNA sequence nGPCR-2101 <SEQ ID NO.71> was identified in *H. sapiens*:
AGGCTGCCTGCTTCGTGTGGGAGAAGCACAGGACTTTCTTAACTGTGAATTGAGCAGCAGCATTGGGTCAC
GGGAAGGACACAGGGACCAGCAGTCACAGCCCCTGGTGCCTCTCTGAGTCCCTCCATCTCGAAGTGCCTGC
CTGGCCCACCTTGTGGTCCTCACTTGGAGCATGCAGTGCTGGAATCTTCTTAGTTTCAGTCTTACTTTGCC
GCCCGAGGTATGTTTTCTCTGCAGCTTCCCTTGCCAAGGACATCCTAGAGATGGGTGATGGAACTTCCAAT
TGTCTTTAAACCCTTTGGATACTGGAAAGCCTGACCTGGGACTGGGTACTTCAGCAGAAATAACACAGGGG
AGAACAGAGTCAAGTCCGGAGTTCAGTTCAGTCATCAGGCAGTGGAGCCACAAGGTGGGGCAGTTTTCCCA
GGTGTCTCATAGTGGCTGACTTGAGCCAGTGACCTCTAAAGATAGAGCAGAGTCCAAGGAATGACCTACAA
AGAGTGAAGGGGACAGGCAAGAGCTGATAGCTTTGGACCAAGACCACGTTCCCTGTTCTGGGTCCATGATG
CTCCCTTCCCCCTGTAGAGGGCAGGTGAGGACCATGTGGATCTTTTTGGAAATACATGTGGATGTTTGCAA
ATGCAGAACCGACTGGTGGAAAGGGCGAACATGAACAGATGATGGGAAGTCTGGCCCTCATGGACCATAT
G

The following amino acid sequence <SEQ ID NO.181> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.71:
YGPMRARLPIICSCSPFPPVGSAFANIHMYFQKDPHGPHLPSTGGREHHGPRTGNVVLVQSYQLLPVPFTL
CRSFLGLCSIFRGHWLKSATMRHLGKLPHLVAPLPDDTELRTLCSPLCYFCSTQSQVRLSSIQRVRQLEVP
SPISRMSLAREAAEKTYLGRQSKTETKKIPALHAPSEDHKVGQAGTSRWRDSERHQGLLLVPVSFPPNAAA
QFTVKKVLCFSHTKQAA

The following DNA sequence nGPCR-2102 <SEQ ID NO.72> was identified in *H. sapiens*:
CCACAAGTCCTTCCTCTTCACACAACAAACAATATTTCTACTAAAATACATAAAAGGAACAGTATTTCATC
TGTTAACAGGAAAAACCAAACTAAGGTCTCCTTATATTTGGCAAGGGAAAACATTCTTTGGGTGTTAACCT
TGGCTCTTGACACTTGACAACTTCCTACAGAATGTCATCCATGTAGAAGGTGATTGAGTTAATTAGTTGCA
AAAAGAAGGGAAAATTAAATTAAGCAGAGTTGAAATATTAATCAAAGGTATACTAAAAAGTTGGTATGTTA
GTGTTATCCACTCTATATAGATATGTTCAGGTGATGTTTTTCATATACCATTGACTTTTTTTGTGTTTGT
TTACTCTGCCATGTTCCAGGATGCCAGGATGCAATATTCTTTCAGGCTTCTTGATAACACTAGTTCTAATT
ATTCAGTAATCTAAAAAATTATCCATAGTAGAAGCATATATGCTTTATTTGGGGTTGAAGGGTTGGACATA
TATGCTTTTTCTGTGGATAATTATATTTATTTTGGGTACATTGGAAAGTATTTAACACAAATTTAGTGGTA
TTAGTACTAGCAAGT



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The following amino acid sequence <SEQ ID NO.182> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.72:
TSPSSSHNKQYFYNTKEQYFICQEKPNGLLIFGKGKHSLGVNLGSHLTTSYRMSSMKVIELISCKKKGKLN
AELKYSKVYKVGMLVLSTLYRYVQVMFFHIPLTFFVFVYSAMFQDARMQYSFRLLDNTSSNYSVIKIIHSR
SIYALFGVEGLDIYAFSVDNYIYFGYIGKYLTQIWYYQ

The following DNA sequence nGPCR-2103 <SEQ ID NO.73> was identified in *H. sapiens*:
CATTGCTGTGTGTGTATAAGTGAATGACAGTGTGTGTGTGTGAGAGAGAGAGAGAGAATATATGCTTTC
TTTTAAAGGTATTGTTCAAGTGAAAACCTTCATTTTAAAATATAAAATGAGTGGCTCATTAAGACCCTAGA
GGTTCTTTTAAGAATACAAGAGGATCTCTCATTTTCATTTCCTAGAATTTCACACACAATACACATGCACA
GTACACACGTGCCTGTGCGTGCATGCACACATACACCCCCCACCTCTGCTAATAAAGCAAGGCCCTTTCTC
ACTAACATAAGGCAATGATAAAATCAATATTCATATTCT

The following amino acid sequence <SEQ ID NO.183> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.73:
EYEYFYHCLMLVRKGLALLAEVGGVCVHARTGTCVLCMCIVCEILGNENERSSCILKRTSRVLMSHSFYIL
KRFSLEQYLKKAYILSLSLSHTHTVIHLYTHSN

The following DNA sequence nGPCR-2104 <SEQ ID NO.74> was identified in *H. sapiens*:
TTGTTTCAAATTGCCAGCTGCTTATGTCAGACTGACTCCCTTATTATGCCTCCAGTAGGCCTGTCAATATG
GCCAAACAGCTAGATAAGTGCGGGGCAGGACAAAGGGCTCTTTGCACAGCAGGGAGGCAATGTTGGTGGGG
GAGGGGCAGGAGGTAGGAAAGGCAAGAGGAGGAGGTTCTTTTCCCTGGGAGATTATTCAGTTTGGCATACA
ATTAAAGAAATCATTTTTAGTTCCCACTCAAGCATTGAATTTTTGCCAACCACATACTATTAACCCCAAAT
TTGATACATTTCAGAATATCTTGTAGGGATCCATTCTCGCCAAGGAAAAATAAAAAAATAAATAAAGCTCT
GTATAGGTTAAAATAAAATAAATCCCACACTCTGCACCCTCCTAGGTGCAAGTCACCTCCCGAGGAGACCC
GTTCTAGAGCTGAATTCTCATTAAGAAATGGAAAAGAATACTCTATCTGAATAAAAACACATTGTAATACA
ATGTGTTTATTTGGGTTGGGATTGGACCTGAACATGTAG

The following amino acid sequence <SEQ ID NO.184> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.74:
YMFRSNPNPNKHIVLQCVFIQIEYSFPFLNENSALERVSSGGDLHLGGCRVWDLFYFNLYRALFIFLFFLG
ENGSLQDILKCIKFGVNSMWLAKIQCLSGNKFLLYAKLNNLPGKRTSSSCLSYLLPLPHQHCLPAVQRALC
PAPHLSSCLAILTGLLEAGSQSDISSWQFET

The following DNA sequence nGPCR-2105 <SEQ ID NO.75> was identified in *H. sapiens*:
TCCCTGGTGCCAAAAGGTTGCAGACTGCTGTTGTAGATGATGAAGAGACACAGCCAAGTTAAGTGACTTGC
CCAAGAACTGTACAGCTAGGAAGTTCCAGAGCCTGCCCTCTTAGCTGCTTCACTCAAGCTTCCTGCTATGC
TAGAGTACCATGCTAACAGCAGGACTACAGACACACATGAAACAAAAAGAATGTAAAATGTCACATCTGTT
CCAATAATGTGAAATGCCAGGAGCTGAGAGACTGCTATGAAGGGCAAGTCTCATGGGACATTTTTTCCAAT
GACTTTTGTGGCTGGTGAACTGTGGTCCTGCGGATGTGCCATAAAAAAGGAAAGCATTGTTTTCTTCCCGC
AGATCATCTTTAAGTTCTCAGAGTTACCATTTGACTTGACACCATTTATACATGCCATGAAATCATTTCAT
TACTTGCTGCTAGTACTTTTTGGAGTAATAACATGTATAAATTTGGTCATAACTAGAGATACATCAAAATC
TATCTGGCTTCCATTTCATCTCTTGAAATACCAGAAGACCAAATGCTTACTTCCTGGTACTTTTGTATAAA
AAACAATTACAAAATTGTGAAGGTTACTATCATTTTTCATCAGCACCATAAAATCAGTAACAAAGATAAGA
CATTATTCAGATCTACTATAAAAAACTACATTGGA

The following amino acid sequence <SEQ ID NO.185> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.75:
SLVPKGCRLLLMMKRHSQVKLAQELYSEVPEPALLAASLKLPAMLEYHANSRTTDTHETKRMNVTSVPIMN
ARSETAMKGKSHGTFFPMTFVAGELWSCGCAIKKESIVFFPQIIFKFSELPFDLTPFIHAMKSFHYLLLVL
FGVITCINLVITRDTSKSIWLPFHLLKYQKTKCLLPGTFVKTITKLRLLSFFISTIKSVTKIRHYSDLLKT
TL

The following DNA sequence nGPCR-2106 <SEQ ID NO.76> was identified in *H. sapiens*:
AAACATTTTCAAGCCCCTATCTAGTCAGGGCTATCAATTAAAAGTATTTATAGGGAATGTGTACTAATATA
TGTCTAAATTTCCTTAGGCTGCCTTAAGGACCATAGGCCAGGTAATCTGTCCCCTCATCCTTGTCACTAGG
ATCAGAGTTCTGTTACAAATATGGAAGGAGAAGTTAGATCACTGTCTGCTCTATTATTATCATCCAAATGT
CTACAGATGAGGAAACTGAGGGCCAGAGTGGTCTAAACCAAGGGCATATGGTTAATAGGAGGTAGAGCTGA
GCCTTGAAGTCAGGTCTGCTTGTCCTAAAGCCTGTACTTTAGCCACTATATTATCCTATTGCATGCTCTAT
ACCACCTTTCTCTGTCTCTGTCTCTGTATTTCTATCTGTCTCTCTCAAGAAGTATTTTTTTGCTAATAAT



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TAAATAATGTGGATTTTTTGTTGTTGTCATTCTTCTTAAAGAACTGTCTTGCTGGGTTCAGTTAGCTCTAA
CCGTGGCTTCTCTACTCCGAGAGCCT

The following amino acid sequence <SEQ ID NO.186> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.76:
NIFKPLSSQGYQLKVFIGNVYYMSKFPAALRTIGQVICPLILVTRIRVLLQIWKEKLDHCLLYYYHPNVYR
GNGPEWSKPRAYGEVELSLEVRSACPKACTLATILSYCMLYTTFLCLCLCISICLSQEVFFLLIIKCGFFV
VVILLKELSCWVQLALTVASLLREP

The following DNA sequence nGPCR-2107 <SEQ ID NO.77> was identified in *H. sapiens*:
TTTGTTGTAAAGATATAAAACAGTAAAATCCCATTGCTTAAATGGGATTTTATATGTATATAAATGGAGGA
AAAGTAACCACGATACACACAAAAATATGAATAAAGTGATTTGAGCCTAGGTAGTAGAAATATGGATTTTC
TTTTTTGTATTTTATATGTTTCCTAAATGTTCTATAAAAAACAAATCTTACATTTACGTAAGAAAAAATAAG
AAATAAAAATTATTCACAATTGAGACTTTTGGTGTTCAAAATACTTGAACATTACTAAGAATGGGTACTAT
GCAGAAACAATTTGTCATTAGCAGATTACCTATGCTCCTTTGGAGTGATTTCTCTGTGACTTTTCACACTA
TTTCACAATTCTGTCCTAGGCTTTATCAAAATCCATGGACATCTGATCGAAACAAAAATTAACAGCAATCT
GCAAAAGAGCTATTAGGGACATTACTCTTGTGAATAGATAGTCAGCACTCTGGGGACAGACACTGTGTTAT
CTTTCTCATCTTAAATTTCACTGCTGGGCTTAACGGTGCTTTGTGCCTACCAGTGTTCAATCATTGGATTC
AATGTTGAATGACTGTTAAACTCCTTGATGTCAGAGCTAATTGCTGACAACACCCTACAGGGTTTGCTATG
AGATGTATATAAATTGCAATCT

The following amino acid sequence <SEQ ID NO.187> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.77:
IAIYIHLIANPVGCCQQLALTSRSLTVIQHIQLNTGRHKAPLSPAVKFKMRKITQCLSPECLSIHKSNVPN
SSFADCCFLFRSDVHGFSLGQNCEIVKVTEKSLQRSIGNLLMTNCFCIVPILSNVQVFTPKVSIVNNFYFL
FFLRKCKICFLNIETYKIQKRKSIFLLPRLKSLYSYFCVYRGYFSSIYIHIKSHLSNGILLFYIFTT

The following DNA sequence nGPCR-2108 <SEQ ID NO.78> was identified in *H. sapiens*:
ACTCTTTCTGTCCATCTGGAGCTGGCGAGCAGCTGGATAAAATCAGGGGAGTTGATATACTTCGTTCTCTA
AGTAGCTCACCACCTTAACACTCCAGCCCAGCCAGGAGCTGTTTCCCTGGATGTACGCTGGTCTGTGTCAT
CTCATCTTCTCCATTATTCTTCAGCCTTCTGGCTGGGGGCTTGGAATTTTCACCTCCTATGAAACAAGTGT
CTGAGAATTCATGAGAAGAGACTGCCACACTAGGGCAGAGCACCTTCAATAGTCAGAGACTGAAATTAACC
ATAACCAGACAGCCTGCATGCCTGCAGTCAAATTATTCATATTATAGAGGAAACACAACAGCAATTTTGTG
ACTGAAAAAGATTGCTTAGATCACGCCTTGGCAAAACCATAAACAAGAATTAGGAACAAACAAAAAACAAA
ACAAAACAAACACAGTGCGCTTTATAGCCCTCAGGATGTTCAGCTGGTGGTGGCTCACATCTGGACTGTAT
GCCACCAAGAAACATTGAAATGAGTCTTTGCTAGAGGCTCTCTCTGAGAGCCAAAAGATGAACTAGTAACT
TCGGAAATGTGCAAATGTGTATCTAATGTGAGCATTCTAAAGCTTGTCTGAGGAAAAGTACTTAAATTGGA
TACCTATGTTGTCCCAAGGGTTTATAATATACAGTTGACTCCTGAATAATGTGAAGATAATGGGTGCAGAT
CTGCCACACAGG

The following amino acid sequence <SEQ ID NO.188> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.78:
LCGRSAPIIFTLFRSQLYIINPWDNIGIQFKYFSSDKLNAHIRYTFAHFRSYFIFWLSERASSKDSFQCFL
VAYSPDVSHHQLNILRAIKRTVFVLFCFLFVPNSCLWFCQGVIAIFFSHKIAVVFPLYEFDCRHAGCLVMV
NFSLLLKVLCPSVAVSSHEFSDTCFIGGENSKPPARRLKNNGEDEMTQTSVHPGKQLLAGLECGGELLRER
SISTPLILSSCSPAPDGQKE

The following DNA sequence nGPCR-2109 <SEQ ID NO.79> was identified in *H. sapiens*:
ATGATGCTTATTAATCATTTGTATAACTTCTTGGGAGAAATGTCTAACACTTTACCCATTTTAATGGGTTA
TTTGTTATATTGTCATTGAATTGTGATACTTATGTAATCTGGATACAAGTTCCTTATCAGATATGTGGTTT
GATAACATTTTATTTCATTGTGTGGATTCTTTTAACTTCCTGATGTTATTATTCATACCACAATGTTTCAC
TTTGAATGAAGTTCAATTTATCTTTTTTTTTCCTTTGGTTGCTTGTACTTCTGGTATTAAATCTAAAAAG
TCAATCATAAAGACTAACTCCTAAGTCTTCTAAGAGTGTTATAGTTTTATCTTCTTACATTTGGGTTCAAT
TTTATTGTTTTGTCAATTTAACACGTATAAGCCAATACATTAATTCTAAGCCAATGAATACATGTTCATTA
GAGAAAAATCAGAAAATATGTACATGAAAAAAAATAAAACAAAATACATTCATAATTCTATTTATTCAAAA
ACAACTACTTCTAGCCTGCTGGTTTATGCTTCCAAACCCTATTTTCTGTGAATGTATTCTAATTTTTGTGT
ATATATGTATAGGTATGCATGTATACATTTTAGTGGGATTACATAATGCACATAGTTGTGTAGACAGGTTT
TTTTCTTTGATATATTGTAAACATATTTGCAGATCAGTTTTTTGGACTTGGCTTTTCTGAACTTCAAGTGT
TTCAGCTGCATAAGAGCAAGTACTTGTGGACAATCAAATGAAATAATGTTATAAATGCACTTTGTA

The following amino acid sequence <SEQ ID NO.189> is a predicted amino



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acid sequence derived from the DNA sequence of SEQ ID NO.79:
MMLINHLYNFLGEMSNTLPILMGYLLYCHIVILMSGYKFLIRYVVHFISLCGFFLPDVIIHTTMFHFESSI
YLFFFLWLLVLLVLNLKSQSRLTPKSSKSVIVLSSYIWVQFYCFVNLTRISQYINSKPMNTCSLEKNQKIC
TKKIKQNTFIILFIQKQLLLACWFMLPNPIFCECILIFVYICIGMHVYILVGLHNAHSCVDRFFSLIYCKH
ICRSVFWTWLFTSSVSAAEQVLVDNQMKCYKCTL

The following DNA sequence nGPCR-2110 <SEQ ID NO.80> was identified in *H. sapiens*:
CTGTGGTCTTTGTTTTGTCCATCTTTCCTTCTTAGGAAATTAAAATAAATACTTGTCCACATTGACCGTAT
CTGCTTCACTATGGCCCTTAGACATAACTTTTTATTTGATGAGTACAGAAATTAGGTCTTCCTCTAACTTT
TCTGTGTTGTTATTCAAATTTATTATCTTCTAAATTCATATCTATGCTATTCCCCCTTTCTATCCTACAGC
ATTTGCATATTCTGCTCTTTGCTCTTCTCAACACAAAAGTACATAGTGATTTCTTTCTCATTCTATCTGTG
CTCTGTTTCTGATTAGCTCTTTGAGTAGGGCCCTTTCTGACTATCAATATTTTTTCAATATCTTCTCACTA
TTTACATTTATTAAATCTCACATTATATTCCACTGCCATTTGATATTTTCTTGAGTTGTTAATAAGTAGAA
CCTTTTTGATATTATATATTTTAAATACAGTGTATTTTTCAAGAGCATGGAAGAAAAAAGTAAGCTTAATT
CAAGTTGTTAATATTCAATCACCCAACAAATGTTTATTAAGCACTGATTACATACCCAGCACTCCTGTAGG
ATCTAGACATGTGAGAAATGAATAAGCAATCAAAATCTCTACACTCACAGAGATCAAATTCTAGTCAGGAG
AAA

The following amino acid sequence <SEQ ID NO.190> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.80:
VVFVLSIFPSEIKINTCPHPYLLHYGPTLFIVQKLGLPLTFLCCYSNLLSSKFISMLFPLSILQHLHILLF
ALLNTKVHSDFFLILSVLCFLALVGPFLTINIFSISSHYLHLLNLTLYSTAIYFLELLISRTFLILYILNT
VYFSRAWKKKVSLIQVVNIQSPNKCLLSTDYIPSTPVGSRHVRNEAIKISTLTEIKFSGE

The following DNA sequence nGPCR-2111 <SEQ ID NO.81> was identified in *H. sapiens*:
AACTCTGTCTTAAAATAATAATAATAAAATAAAATATATATTTATATATGGTATATGAATTTGATACATTT
TGCTTTATTTCAGGACTAATGTAATGCTACAGAAAAGGAATGACTCTAAACTCGCTTAATTTCTCCTGACT
ATAAATAGCCCTTGACCACTTTCAACTTTCCCACTGATAACTCTATAACATAGGGCAAGTTACTTGACCTC
ACTGAGCCTATTTTGCCATCTATAAATCAGCTAATAGGACCTAACTTATAGGTTTGCTGAGAGGTATAAGT
AAGACAATAGAGTCTAGCATATGGTGGGGCTCAACAAATATTAGTACATTACTTACACTTTTTTTTTCACC
CTGCTATGCCTTTCAGTTTATTTCTACTAAACTCTAAGTTATTAAAATACAGGCTGAAGTATTATTAATTT
CCCTCTGTGTTCTCCCCGGTTCCTATCACAGTGCCAGGGACACACAGGCCCCATAATCCTTCATGGTCAAT
TGAACTGACAGTGAACTATGTCTTCGTCCATTTGGGATGCTACAACAAAATACCATAGACCGGGTGACTTA
TAAACCACAGAAATGTGTTTCTTATCGTTCTGGAGGCTGGGAAGTCCAAGATCACGGCATTGTCAGATTCA
GTGTCTGGTGAAGGCCTG

The following amino acid sequence <SEQ ID NO.191> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.81:
LCLKIIIIKNIYLYMVYEFDTFCFISGLMCYRKGMTLNSLNFSLIALDHFQLSHLYNIGQVTPHAYFAIYK
SANRTLIGLLRGISKTIESSIWWGSTNISTLLTLFFSPCYAFQFISTKLVIKIQAEVLLISLCVLPGSYHS
ARDTQAPSFMVNTDSELCLRPFGMLQQNTIDRVTYKPQKCVSYRSGGWEVQDHGIVRFSVWRP

The following DNA sequence nGPCR-2112 <SEQ ID NO.82> was identified in *H. sapiens*:
CAGCCCACTGCTGAGTTTTCATAATAATGGAGGAACAATGGTCTTTGAAGTTACAGATAATCCCCAGTCCT
CATTGTGGTCATCTCTTTCTGTCCAATCTTTCTCTGGAACAACTAGCAAGGATGCAAAATTGACTGATGAT
CTTCTCCCTTCCCCTGCTTGACCCTGCATACACACCGCCTCTCGTAGAAGTGCCAAGGAGCAGTGAAATGA
CCAAAAGGCAGGGAGTAGGAGGGAGAGGAAAGAAAAACAAACCAAGTGATCAACCCCAAATGACTGAGTGT
TGGCTGTTTTCTATTATTTACTCCTTTGAGCTTTCTCAGATGTGTTTTTCTGAGAAGACTTTCATGTTGTC
TTTTCTTTCCTCTCTGATAGTTAACCACCAATTTCCCTGCAATGGGCTAAGGGTGCAGAGCCCTTGAATGA
GGTCCAGGTAGGCTGCCAGATTCTCAAGACACTAAAGCACAACATTTCCATCCCCATTCTTTTGAAAACAG
GCTTTTAAATTGTGCATGAAGCCATGTCAATGATGAACAAAAATGAAAGTCACAAAGTAGTGAGTGAAAAT
TCAAAAGCAGTTCATCCATCCTCGGTATTTACATACAGCTTTAAATATGGTAGATTT

The following amino acid sequence <SEQ ID NO.192> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.82:
AHCVFIIMEEQWSLKLQIIPSPHCGHLFLSNLSLEQLARMQNLMIFSLPLLDPAYTPPLVEVPRSSEMTKR
QGVGGRGKKNKPSDQPQMTECWLFSIIYSFELSQMCFSEKTFMLSFLSSLIVNHQFPCNGLRVQSPMRSRA
ARFSRHSTTFPSPFFKQAFKLCMKPCQTKMKVTKVKIQKQFIHPRYLHTALNMVD

The following DNA sequence nGPCR-2113 <SEQ ID NO.83> was identified in *H. sapiens*:



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TTTTCTCTGCAGCTTCCCTTGCCAAGGACATCCTAGAGATGGGTGATGGAACTTCCAATTGTCTTTAAACC
CTTTGGATACTGGAAAGCCTGACCTGGGACTGGGTACTTCAGCAGAAATAACACAGGGGAGAACAGAGTCA
AGTCCGGAGGTCAGTTCAGTCATCAGGCAGTGGAGCCACAAGGTGGGGCAGTTTTCCCAGGTGTCTCATAG
TGGCTGACTTGAGCCAGTGACCTCTAAAGATAGAGCAGAGTCCAAGGAATGACCTACAAAGAGTGAAGGGG
ACAGGCAAGAGCTGATAGCTTTGGACCAAGACCACGTTCCCTGTTCTGGGTCCATGATGCTCCCTTCCCCC
TGTAGAGGGCAGGTGAGGACCATGTGGATCTTTTTGGAAATACATGTGGATGTTTGCAAATGCAGAACCGA
CTGGTGGAAAGGGCGAACATGAACAGATGATGGAAGTCTGGCCCTCATGGACCATATGTGTTTGGTGGATA
TTAGACCAATATTTGGGAAGAAGCCTTGCAGATACTTTCTCTCATTAGACATTCTACTCTCTGATTCTGAA
TTTGACTACTCTATGTACCTGATATCAGTGGATTCCAGAGTGAATCAGAGTGTAGAATAGTAGTTTCCAGG
AGCTGGGAT

The following amino acid sequence <SEQ ID NO.193> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.83:
PSSWKLLFYTLIHSGIHYQVHRVVKFRIRENVEKVSARLLPKYWSNIHQTHMVHEGQTSIICSCSPFPPVG
SAFANIHMYFQKDPHGPHLPSTGGREHHGPRTGNVVLVQSYQLLPVPFTLCRSFLGLCSIFRGHWLKSATM
RHLGKLPHLVAPLPDDTDLRTLCSPLCYFCSTQSQVRLSSIQRVRQLEVPSPISRMSLAREAAEK

The following DNA sequence nGPCR-2114 <SEQ ID NO.84> was identified in *H. sapiens*:
ATCCAGCAGAAGCGGCGCCGCCACCGCGCCACCAGGAAGATTGGCATTGCTATTGCGACCTTCCTCATCTG
CTTTGCCCCGTATGTCATGACCAGGTGGGTCCTGGCAGTCCGGCTCCTGTTGTGGGAACAGCTGGGTGGGC
TTGGCCTCAGTTGAGTAGGCCTCTGAGGTTTCCCAGCAAGATATCTGGAGGGCGGCCACCACCAGAGGACC
CTCCTCCACACCTGACGGGCTCAGGGCTGTGCTTCAGCTCCTGGGAAAGATCCTGGGAGGGAGGTGGCACT
GGCTCCCATCCTGTCCTATAAATGAGGAGACTCTCCTTGTCCAGGCACAGGCAGATATGGGGTCTGTGAAT
CAGCACCTGGCTCTTTAAACCTAGAAAGCTTTCAAAATCAGGCAACCTGGGACTAACTCAGGCCTCAGACT
CCGCATCTCCTGGGCGTGGAGTTGGGAATCTGGGTGGAAGCTCCAGCTGGAGCCTCGGGGCAGTAACACTG
CCAGGTGAGTGTTCTCTTTGCTTCTCTCTTTCCTGGAGACCTTGGCCTGAGTGCTTGT

The following amino acid sequence <SEQ ID NO.194> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.84:
IQQKRRRHRATRKIGIAIATFLICFAPYVMTRWVLAVRLLLWEQLGGLGLSVGLGFPARYLEGGHHQRTLL
HTRAQGCASAPGKDPGREVALAPILSYKGDSPCPGTGRYGVCESAPGSLNLESFQNQATWDLRPQTPHLLG
VELGIWVEAPAGASGQHCQVSVLFASLFPGDLGLSAC

The following DNA sequence nGPCR-2115 <SEQ ID NO.85> was identified in *H. sapiens*:
GCTAATGCTGTGCTCATGGTAGAGAACCGGAATACAAGCCCTGCTAAGCCCGTTGCAACCACATTAAGCTT
CTGCTTGGATGCAGAAAGGGCATATGTCCTCTCATTCCATTGGCCAAAGTCCAAAGTCAATGCGTCAGACA
GGATCATCTACTCCTCCTGTAGAAGCACAGGAAAGTTATGGGAAAATCGCAAAGGATGTAGAAACAAACTA
CAGAGAGTGAATGAGGAAACACAAGCAAGAACCCAGCCTCAGAAACTTTGCCTAAATACTTATGCATTAGA
ATTACATCAGCTATATGTGTCAGAAAGACCAAGAGAAAATGGCTTAAAACAAAGGGAGAAGTTTATGTCTC
CCTCACCCAAATGAATGGTCCATGCTCAGTATAGACCTTCACAACGTTCAGGACTGAAGCTCTTTCTACGC
TGTTTCTCA

The following amino acid sequence <SEQ ID NO.195> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.85:
RNSVERASVLNVVKVYTEHGPFIWVREITSPFVLSHFLLVFLTHIADVILMHKYLGKVSEAGFLLVFPHSL
SVVCFYILCDFPITFLCFYRRSRSCLTHLWTLANGMRGHMPFLHPSRSLMWLQRAQGLYSGSLPAQH

The following DNA sequence nGPCR-2116 <SEQ ID NO.86> was identified in *H. sapiens*:
TATTTACTAAACCAATCATAATTTCAAATCCCTGAAACAGGGATCTTTGGCTACTTTCTATTAAAGGATAG
AACAAAGCACCTTCTCCAATTCTTATCATTTTTAGTTTTCTTTTTTACTTTCTATCCTTTTTTAACATGTA
ATTTCAGTGCCAAAACAGACTTGCCCATTTGTGCTCACCAGCAGCTTTCCCATAGAGATGAAGATAAGCTG
CCAGCAATTCTTAACTATGGTCTCAATGGGCCATCATTAGAGGCAACACGTGCATGCTGAAGAGTATTTGT
TAACCTTTAACTTGAATTGACAAGCAAGCCCTTAACAAAAAGTCATCTACACAGATTTCTTTCCTAAATGC
CTGAGTTTTATTTTTAAGATTTTAAAAGAATAGCTCCACCTAGCCCTTCATTTTGCATATTTATTTTACTT
AGACTGCTTTACTTACATCTTTCCCCATTCTAGCTCAGAATTTTTATGAGGAAAATTTGAGAATAACAGCC
CTAGTTACCTGTTGGAGTGGTCACCATGCATTCTTTATATGGCAGCTGATTCAATCCCTCTTCCACAACAA
GTCTGATCTAGAGAGTCAAAGGAAGAAGAAGTTGAGAACCTGCTGGGAATCTCCTGTTAGCT

The following amino acid sequence <SEQ ID NO.196> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.86:
FTKPIIISNPNRDLWLLSIKGNKAPSPILIIFSFLFYFLSFFNMFQCQNRLAHLCSPAAFPRRAASNSLWS



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QWAIIRGNTCMLKSICPLTIDKQALNKKSSTQISFLNAVLFLRFKNSSTPFILHIYFTTALLTSFPILAQN
FYEENLRITALVTCWSGHHAFFIWQLIQSLFHNKSDLESQRKKKLRTCWESPVS

The following DNA sequence nGPCR-2117 <SEQ ID NO.87> was identified in *H. sapiens*:

ATTTTGTTTTTTAAAAGCTAGTAACACACACACACACGAGTTCTGCAAGGCACACTATGAAAACAGTAGCT
CCTGTCCACTTCAGTCTTCTAGTTCCCAGAGGCAATTATTTTCTTTTGATTGTTTTCTTTTGGTATTTATC
TCCATACCTCTAAAGCTTATATTGCCACTTCTTGATTTTCCAGTTTTCAACATTGATTTTTCAATTTTTCC
ATGCTGGAAGAAGAGGATTTAACTACTTTCTACTATCTTTCCCCGTCACTCAATATCACACACACACTCCA
TCTCTCACCCCCACCCTCTCAATATTTTCACTTAAATCAATAATCAATATTTACATCATTATAATGTGCCG
TG

The following amino acid sequence <SEQ ID NO.197> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.87:

FVFKLVTHTHTSSARHTMKTVAPVHFSLLVPRGNYFLLIVFFWYLSPYLSLYCHFLIFQFSTLIFQFFHAG
RRGFNYFLLSFPVTQYHTHTPSLTPTLSIFSLKSIINIYIIIMCR

The following DNA sequence nGPCR-2118 <SEQ ID NO.88> was identified in *H. sapiens*:

GGCCTGTTCCAGACACCTTAGAAGGCAGGGCTGGTCCTGGCAGTCCACACAGAACTGCCGTTCTTTTCCCC
AGAACTCTCTCCAAGCCGCTCCCTTCTTTGGCTTCTCAACATCTCTGGGAATATGTGGGTGCTGTTGCCCA
CATGTGTCATCGAGACACCCCTGGCCATGGAGCTTAGATAACTTGCCTGAACTCATACAGCTAAGAGGAGA
CAAAGGCAGGGTGTGACCCTGGGAGGTTGAGCTCCTTACCCCACTCTTCCCCACTGCCCTCCATGGCACCC
GCAGTGGTTTTTCTATTTTGGTGCTGAGTTCATCCTGTCTTGGGTTACAGCTTGGTGCTTGAGTATCTGTC
TTCCTCGTGATTTCCTGAGGGTCTCTTATTTACAAGAAACCATGCCACAAATTGAGGAACCACAGAATTCA
AGAATGAATTGAAAAAGCCCTCACCCTCAGGAAGTGTGCACTGCTGTGTAGCTATGTGTGAGTTTATAAAT
AGGTACAATAGAGGATAGAGGGTGAGGAGCCCTCACTGGTGGTACAGGGAGAACTGGTGAGTTCCCACAAG
AGAATGGCGTCCGCCCAGGAATGGGGGAGCATCAGCTACACCTCCTAGATCAAGGACTGTGTCCCTTGACC
ACACCGTTTATCCTGCAAGACACTGATTTTTACAGGTGCC

The following amino acid sequence <SEQ ID NO.198> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.88:

APVKISVLQDKRCGQGTQSLIEVLMLPHSWADAILLWELTSSPCTTSEGSSPSILYCTYLTHTLHSSAHFL
RVRAFSIHSILWFLNLWHGFLIRDPQEITRKTDTQAPSCNPRQDELSTKIEKPLRVPWRAVGKSGVRSSTS
QGHTLPLSPLSCMSSGKLSKLHGQGCLDDTCGQQHPHIPRDVEKPKKGAAWREFWGKERQFCVDCQDQPCL
LRCLEQA

The following DNA sequence nGPCR-2119 <SEQ ID NO.89> was identified in *H. sapiens*:

CAAAACAGCTGAATGCTGTGTGAAGCCTCTTGTATAAAGTTCTTAATCCCATTTAGGAGGGAGGAACCTTC
GTGACCTAATCACCTCCTTAAAGGCCCCACCTCTTTAATACTGATGCACTGGAGACGTTTCAACATGAATT
TTGGAGAGACAGAAACACCCAAACCATAACAGAAATGAAAAGGGAAGGGAGTGATAGGTTGCAGAAAAGGG
AGAGGTTAAGGATAAATGAGATGTGAGTAATGAAATAAGAGAACCAGATGATTATTAAGAATATGGTATAC
CATAGTCTGACTTCACTACTGGAGTATTTCTGGATGATGCAGAGTACAGACGAAGGGGCAGGTGGCTAAAG
TGAAGTAGAGATGAGGGTCCATTGTAGTTGACAGGTCAACTAATTGGGATACGCATGTTTTGAGATAGTGA
TCTACCTGGACATTGAAAATGATCCAGGATAAGGGTGCATCTTTATACGAAGAAGGTGACTCCCTATTTTA
AGATGCTGTCAACAGATAATTGGTCCACAAAATGGGCAGAAGAGGAAGGGAGTAGACAAAGGACTGAATAT
GTTATCTTTATCCCCTACTACACCCGTGGTTGAAATTGTATAAACGAGGAATAGTAAA

The following amino acid sequence <SEQ ID NO.199> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.89:

LLFLVYTISTTGVVGDKDNIFSPLSTPFLFCPFCGPIICQHLKIGSHLLRIKMHPYPGSFSMSRITISKHA
YPNLTCQLQWTLISTSLPPAPSSVLCIIQKYSSSEVRLWYTIFLIIIWFSYFITHISFILNLSLFCNLSLP
SLFISVMVWVFLSLQNSCNVSSASVLKRWGLGGDVTKVPPSMGLRTLYKRLHTAFSCF

The following DNA sequence nGPCR-2120 <SEQ ID NO.90> was identified in *H. sapiens*:

AGTGCAATTGTTATTTTTCTTTCGTCTTTTCTCTGTCATTTTCTGTTCATTTTTGGGAGAAGAATGCTAAG
TTACTAATATAAGTAGCCTTATAAATGTAAACTCATAATTGTCAGGAAATGTTACATAAGCGAATGTCTTC
TGCGTCTTTCAACTTTTTGGTGCCCTTATGCTGCCCCCTGCTGTCCAGTGTCCACACTTACTGAAAATTGT
CCCAAACTTCCAACCTTTTCTACTTCTCTTTACTCCGCCATCAAAACTTACCTGGCAAGAGACCCAGACTG
TTGGAGTTTCCCTCCACAATGCCAATGGGTTAACAGACAAATAAAAGAAAGAAGTAGTTCTCTCTTTATTT
ATCCCTTCATCATTTTCTGGCAATTGACGCAAGCATTTGAACTGGTGCTCTGTGGGCAATGCCTGATTTCT
AGGTTCCCCAGCTTGGGATTCCAAACCCTCCCTGTGTTAGTCCAAGCTACTCTCATGGACCTGTCTCTCCC



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AGTGTCTAACCTCTGCACATCATACCCTACTCTCTATCCGCACTGGCTTCTAGCTGTGTTTCCCACAGCCA
CGTGTGTTCTTCCATCTTTGCCTGTGCCCACACTGC

The following amino acid sequence <SEQ ID NO.200> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.90:
SAIVIFLSSFLCHFLFIFGRRMLSYYKPYKCKLIIVRKCYISECLLRLSTFWCPYAAPCCPVSTLTENCPK
LPTFSTSLYSAIKTYLARDPDCWSFPPQCQWVNRQIKERSSSLFIYPFIIFWQLTQAFELVLCGQCLISRF
PSLGFQTLPVLVQATLMDLSLPVSNLCTSPTLYPHWLLAVFPTATCVLPSLPVPTL

The following DNA sequence nGPCR-2121 <SEQ ID NO.91> was identified in *H. sapiens*:
TCCACCAGGTGCCACCGCTGCTCCGTACCATGGCCAGGTCCATTTTGGAGGCACCAGACCCATGATAAAGC
CCAAGCTGTGAGGAAGGAGAAAAATTTAGTGCTCTCCTCTTTCTTGCAGTCTGAAAGATGGATGTGTGTAA
CCTTGAGTCTTTTAGAAACCTTAATAAAATGGTTTTTACTCATGGTCCTTCTCTCCCTAAGAACCCTTAGA
GCTGGGGTGGGAATGAATTTATGTGACATCTACTAGGCATACTCAGAATCATTGCTTTCCTCCAAGAATGT
GGTCAAACTGGAGCCTGTCTTTTTCCTTTCTTCCCAGGAAGACCTCAGGAAATCTCAGTGAAGTTGTACCA
AGTTTTCTTGCTTTATTAACAGATCTCCAGCTATCTCAACATGATTTTGGCTTAAATTATATATATTTACT
TATCATAATGACTGTTTAGTTAATGACTTCCTGTCATATCAGCTTTTAGAAAGCTATACCACTTTTAGGGC
AACTGTTTCTTTTTTACTATTTCTCTATTGGATTTTGGTACAATTTTCTCACCCCAAAACACTCATGGCAT
AGTATAATATAATATAACCTATGCACATCCTCTCATATACTTCAAATCATCTCTAGATTATTTATAATA

The following amino acid sequence <SEQ ID NO.201> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.91:
STRCHRCSVPWPGPFWRHQTHDKAQAVRKEKNLVLSSFLQSERWMCVTLSLLETLIKWFLLMVLLSLRTLR
AGVGMNLCDIYAYSESLLSSKNVVKLEPVFFLSSQEDLRKSQSCTKFSCFINRSPAISTFWLKLYIFTYHN
DCLVNDFLSYQLLESYTTFRATVSFLLF [illegible]ILVQFSHPKTLMAYNIIPMHILSYTSNHLIIYN

The following DNA sequence nGPCR-2122 <SEQ ID NO.92> was identified in *H. sapiens*:
CAAAGACATACCAAGTACTTCTCATCTTTCTTGCTTTGAAAGCCTATTTCCTGAAATGGATTTCAGAGCCC
TTCACCCCTAACTTCATTTTTCCTTGAGCCTGTATCTTTATGGTAATAGCTACAGCCTCAATTCCCAATCA
CCTATGAAAGGCAGACACTTTATGGACATTTTCTTATGAAATCCTCTGTACTTATGAACTTTCATAGATGT
GATGTTCAGTCCCATTTTACAGATGACGTTTCCCAGAGTTTCAGTAAGTTGCCCAGTTTCTAATTTTAAAA
TACTCAATGTGTGTGTGTGTGTGTGTGGTTTGGGGTAGAATGCAGTGCTCAGAGAACCTTAACTTTAATGC
TAAATATGTGGCAAAAGAATCTTGAGATATTATTTTTCTCTTGATAATTTCTGTGATTTCTTTTCAACTCT
ATCCCCAATCAGAAAAGGTCCTTCTGGGCCAAAAATGAAGAGGTAGATTTATGCCAGTTAAGGTGTGGATC
ATGGAAGAGGACCCATGGGTATGACTAGT

The following amino acid sequence <SEQ ID NO.202> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.92:
TSHTHGSSSMIHTLTGINLPLHFWPRRTFSDWGSKEITEIIKRKIISQDSFATYLALKLRFSEHCILPQTT
HTHTHIEYFKIRNWATYNSGKRHLNGTEHHIYESSVQRISENVHKVSAFHRLGIEAVAITIKIQAQGKMKL
GVKGSEIHFRKAFKARKMRSTWYVF

The following DNA sequence nGPCR-2123 <SEQ ID NO.93> was identified in *H. sapiens*:
AATAAGTCTAGCAAGGGAAATATTTTTAGGTGTTTTTATTATTTTTTATTTTTTATTTTTTTGCTCTGGAA
ACTGTTAGTCCAAACTGCACCATTTTGTAACCCCCCAGCCATTTCGCAGACCTCGGTCAAAGTGAAACATT
CCACAGGGGTTCGGGCTGTGACAAACAGCCTGCCCAACCGCTTGACTCTCTTATTATATTCTGCTGGAAGA
AAGTGTAAGGAACCTCACACTGCACTGGAACAGGCACCAAACTGCCTAATCATGGGAACATGTTATCAACA
TTTTCCCAGGCAGCAGGCCATGCCCCCTGTTCCAGACCCCTCCCACCTAGCCTATAATTGCCCCAGCCTGT
AAGTGGCGATGGCCATTGGCATTAAGCTGCAGGTCTTATGCTGGACATAAAGCCGGCATTTGCTGTAAAGC
CACCACTCTCTCTCTTTGTGTCTTTCTTTAACCCTAGCCTTCCCTTCAAAACCCAACAAAAACTATTTATA
AGACAATTTTTCTTCATCCTCCAGTAAGAACCTAATTTTTTGTTTGTTTGTTTTGGTTTG

The following amino acid sequence <SEQ ID NO.203> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.93:
NKSSKGNIFRCFYYFLFFIFLLWKLLVQTAPFCNPPAISQTSVKVKHSTGVRAVTNSLPNRLTLLLYSAGR
KCKEPHTALEQAPNCLIMGTCYQHFPRQQAMPPVPDPSHLAYNCPSLVAMAIGIKLQVLCWTSRHLLSHHS
LSLCLSLTLAFPSKPNKNYLDNFSSSSSKNLIFCLFVLV

The following DNA sequence nGPCR-2124 <SEQ ID NO.94> was identified in *H. sapiens*:
CTGCTTTATCTTGGGATTCCAGTATATCAGCAGGGAATTCCATGCATCCACTCCTGGCATATCCTTTTGTG



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GTGAGTCTGCTAATAGCCTGTGTCATTTTGAAGGAGAAGACGTCTGCCAGGCCATGATGTGATATGTACTC
AGTGCAGCTGGTGTTTGTCAGCCACAGGCCCCGCCGCTCCACTAAGCTTCCATTCCTCCTGTTCCTCCTGT
GTTCAAGAATGTGGAGCCTGCCTCCCTCTGGGCTCCAAAAATGCTTCAGGCTGGGTCCTGTAAAATCTTAA
CATTTCCTCCCACCCCTATTCCCTTAGCATTGCCACCTTTTTCATAAAATAATTTATACAACTGGAAAGGA
AGAAAAAAAATCCAGTGCAAAAATACCATACGTAGAACAACATTATGAAATCTCCTTAATGTCCTGAAAGC
TGCACCAGGCCATTTGGAAGATGCATTAGCTAGATAAGTATTAACAGAAGGGCCTATCACAGAAACGTTAC
CCAAACTACCACCTTTTATTAAGCCCCCAGGAGAACTTAAAACCAGCCCATTACTCTGATGTCTGAGACGG
GCCT

The following amino acid sequence <SEQ ID NO.204> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.94:
ARLRHQSNGLVLSSPGGLIKGGSLGNVSVIGPSVNTYLANASSKWPGAAFRTLRRFHNVVLRMVFLHWIFF
LPFQLYKLFYEKGGNAKGIGVGGNVKILQDPASIFGAQREPGSTFLNTGGTGGMEAWSGGACGQTPAALST
YHIMAWQTSSPSKHRLLADSPQKDMPGVDAWNSLLIYWNPKIKQ

The following DNA sequence nGPCR-2125 <SEQ ID NO.95> was identified in *H. sapiens*:
CTTCAAAATTGTAAGCTTATTTTTATATAAACCCTCCTAAAGATAATTGCAGAAGTTCAAGTAAAATACCT
GACATGAAGTTGGCAATTGCATTCATTTTCTATCGACACAATAACATAGTATGACAGACTTAGTAGTTCTA
AACAATACAAATTTATTATCTCAGAGTTCTTTAGATCAAAAGTTCAACATAGGCTCCTGAGCTAAAATCAA
GGGTCTGTAGGCCTGTGCTTCTTACTGAAGGTTCTAGGGAAGAATCCACTTTCAGGTTCATGCATATTGTT
GGCTGAATTCTATTCCATGCAGCTATAGAATTTAAATCCCTGTTTTCTTGCTGGCTAAAGGTCTGAATCAT
TTTTTACCTTTAGAGATTGTCTGCTTTCCTTATCTTATGGCCCTTTTATCTTCAAAGTCAGCCATCATGAT
TCAAGTCCTTCCATAATTCATCTCTTCTGTCATCTATTCTGACATGTCTTCTCTGCCAAGTCTTCACTGAC
TGACTCTTCTTCCTTCTTCTATTTGTAAAGGCCCACATACTAATCCAGAATAATCCCTCTATTTTAAAATC
AACTTATTAGAACCTTAATTCCATCTTCAAAATTGTGTTTCCATATATCATAACATATCCACAGGCATTTG
GCACAAGAGGGTGACAATTATGGCTTGTGTTAGCCATAAGATAACAGCACCTAACAGGTAAATAACC

The following amino acid sequence <SEQ ID NO.205> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.95:
FKIVSLFLYKPSRLQKFKNTHEVGNCIHFLSTQHSMTDLVVLNNTNLLSQSSLDQKFNIGSAKIKGLACAS
YRFGRIHFQVHAYCWLNSIPCSYRIIPVFLLAKGLNHFLPLEIVCFPYLMALLSSKSAIMIQVLPFISSVI
YSDMSSLPSLHLTLLPSSICKGPHTNPESLYFKINLLEPFHLQNCVSIYHNISTGIWHKRVTIMACVSHKI
TAPNRITSKLAYFYINPPKDNCRSSSKIPDMKLAIA

The following DNA sequence nGPCR-2126 <SEQ ID NO.96> was identified in *H. sapiens*:
ATGTGCCCTGGTGCTTCCAGGAACTAGGTGGCCCCCCACCCACCCCGGGGCTGGGCACCTTACCCAGGGGA
GAGAATAAGCTGTGAAGCTGGTCCTAGGGTGCGAGGATGGCTGGCCGGGGTTGGGCTGGGAAGGAGAGGCT
GGCCAGGCTTCTTGCTCCTGCCCCCACACCTTCAGCCTCTTCCCCAACCCTTTAGCCACTGCTTACCCAGC
AAAGGCCACCAGGGCCACAGCGGAATAGGGAGCCCAGGAGAGCACGAAGAGGAGGATGACCAGCAGCATGA
TCTTGGCCATCTTGCACTCGCTCTGCAGCCGCTGCCGCTGCCACAGGGACTCGCCATTGCCCTTGCAGGCC
CCGAAGGTCTGGAGAGCCCTAGGAAGGACGCATCGTCCAGGTCTGACCCTAGTCGGGTGGCAGTCAGCACC
AGGGTCACGGCTGCTGTTGGGGAGCCTCTCTGGACTATCCTTGCAGGGCACTCGTGAGAGTGTCATTCCTT
CCAGTGCAGGCAGCCCTGACTTCCAGAAAGTTTTCTGTGACATGAGGTCTCAGCTGCCCCCTACTCCCTCT
TGATTCTGTGTGCCTTCTCTCCTCCCTCTGCCATGCCGAAAAGCCCGCCCCAGAAGCCCTTGTCTCCTGAG
GCTCCCCTAGACACTGCTGCCCCATAAGCACTTGCTCAGCTTGCCTTCACCCACTGGTCATGCTCTGGTAG
GCTGGTGCAAGTGTGAGTGGTGG

The following amino acid sequence <SEQ ID NO.206> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.96:
HHSHLHQPTRAPVGEGKLSKCLWGSSVGSLRRQGLLGRAFRHGRGRREGTQNQEGVGGSDLMSQKTFWKSG
LPALEGMTLSRVPCKDSPERLPNSSRDPGADCHPTRVRPGRCVLPRALQTFGACKGNGESLWQRQRLQSEC
KMAKIMLLVILLFVLSWAPYSAVALVAFAGAVAKGLGKRLKVWGQEQEAWPASPSQPNPGQPSSHPRTSFT
AYSLPWVRCPAPGWVGGHLVPGSTRAH

The following DNA sequence nGPCR-2127 <SEQ ID NO.97> was identified in *H. sapiens*:
ACATCGTATCTTTTAAAAGGCTTTTTAAAGCTGATAACAAGTTACCTTTGATTGCATATAAAACTCTATAT
TTTTCCTCCTCTAACTCATCTTATGTTTCTGATGTCACAATTTACTACTTTTATATTGCATATGCCTTAAC
AAATTATTGAATCTATTATTATTTTTAATAGTTTTGTTTTTCAACCTTCATACTAAAGATATAAGTAATTG
ACATATCACCATTACAATATTAAAGTGTTCTGAATTTGACTATGCATTTACTTTTGCTTATAAGCTTTATA
CTCTCTACGTTTATGTGTTAGTAATTAGCATCCTTTTCTTTCAGGTTTTTTCCAATATAAAGAACTCTATT
AGCATTTCTTGTAAGACAGGTATGGTGTTACTGAACTCTCTCAGCTTTTTTTGGGAAAACCTTTATCTCT



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TTTTTATTTCTGAAGGACAGCTTTGCCATGTACAGTATTCTTTTTTGG

The following amino acid sequence <SEQ ID NO.207> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.97:
HRIFKAFSQVTFDCINSIFFLLLILCFCHNLLLLYCICLNKLLNLLLFLIVLFFNLHTKDISNHITITILK
CSEFDYAFTFAYKCICLNKLLNLLLFLIVLFFNLYTLYVYVLVISILFFQVFSNIKNSISISCKTGMVLLN
SLSFFLGKPLSLFLFLKDSFAMYSILFW

The following DNA sequence nGPCR-2128 <SEQ ID NO.98> was identified in *H. sapiens*:
ATACATACCATGAAATGGTTATGGAGGGAGATAAGGGATTTAAGAATTGCTCCAGGTTCTTCAGAGAGAA
CTGAGCCTCTGTTGTCTTTACTCAAGAAGTTGATCTCTAGTTAGAGAATGGCATTCATTCATACTTTCATT
CATTCAGTTATTCATTCCTTCAACAACTTTTGGAAGGTACTTTCTGTGTGACAAACACATCACAAACAACT
GTAATATAGGCTGCAGATACGAAAACATATTTGCTGCCATGATGTAGAAAAAATCACTGCAAACATTTTAA
AAGTTTGGAAAATATAGCTCAGATTGAATTTTTGCCCTAAGATAAAAAAAATCATTGGGAGATAAAAGCAA
TATATGAACATGGAGTTAATAGATTTTTTCCCTTTTAACATAGATAACAGTACATAGTGATTCATTTGTCC
TCTGTCATTTGGTCTTGAGGAACACTAATGCCCTAATATGTGTAATGTTCAGTAACAAATGCTAAATAAAA
ATACAGGAATAAAAATCCATTAAGCATGTATTTAATACTGTGTAACACTTACTGT

The following amino acid sequence <SEQ ID NO.208> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.98:
TVSVTQYIHAWIFIPVFLFSICYTLHILGHCSSRPNDRGQMNHYVLLSMLKGKKSINSMFIYCFYLPMIFF
ILGQKFNLSYIFQTFKMFAVIFSTSWQQICFRICSLYYSCLCVCHTESTFQKLLKEITEMKVMNAILLEIN
FLSKDNRGSVLSEEPGAILKSLISLPPFHGMY

The following DNA sequence nGPCR-2129 <SEQ ID NO.99> was identified in *H. sapiens*:
CCTGCTGGCCGGAGCAGCGGCAGGGAAGGTAGACGACTGCAAGGCATTGGAAACGGCCCCTCTGCATCAGG
AGGACACCCTGGGTGCAGGAGGAGGCTTCGCTGAAAAGCATTGCAACAGCATTATCACATACGTGGAAATA
AGAATTGCATCTCAACCCTTCCCTTGCCCTCCACCCATCTAACATGCCTCAGCCCTCCTGTGGCCATAGTA
ACCTGAACAGTAACTACAGCAGCAGGCTGCTTAGGTGCCAGGTGTAAGAAGAGAAATTTCATGAAAACAGG
AAAATATAGCCTGCTTTTCTCCCCAGCTCTAACCTTTCAACCTATAACTACTCCCTACTGTAATTTTTGTG
GGATTTGCTGATATTGAAGGAAGATGATTGAAAATCTGCTTAAGATTTCGTCTTTATTTCCCGCTTGACAG
GCCTAGGGCCCCACTGAGGAAGTGTTTCTCTCTGCAGAGCCCTCAGCCACCCCATATGTCCCAGGGATGTG
CTCAAGTCACGAGGACC

The following amino acid sequence <SEQ ID NO.209> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.99:
GPRDLSTSLGHMGWLRALQRETLPQWGPRPVKREIKTKSADFQSSSFNISKSHKNYSRELVERLELGRKAG
YIFLFSNFSSYTWHLSSLLLLLFRLLWPQEGGMLDGWRAREGLRCNSYFHVCDNAVAMLFSEASSCTQGVL
LMQRGRFQCLAVVYLPCRCSGQQ

The following DNA sequence nGPCR-2130 <SEQ ID NO.100> was identified in *H. sapiens*:
CAAAGACATACCAAGTACTTCTCATCTTTCTTGCTTTGAAAGCCTATTTCCTGAAATGGATTTCAGAGCCC
TTCACCCCTAACTTCATTTTTCCTTGAGCCTGTATCTTTATGGTAATAGCTACAGCCTCAATTCCCAATCA
CCTATGAAAGGCAGACACTTTATGGACATTTTCTTATGAAATCCTCTGTACTTATGAACTTTCATAGATGT
GATGTTCAGTCCCATTTTACAGATGACGTTTCCCAGAGTTTCAGTAAGTTGCCCAGTTTCTAATTTTAAAA
TACTCAATGTGTGTGTGTGTGTGTGTGGTTTGGGGTAGAATGCAGTGCTCAGAGAACCTTAACTTTAATGC
TAAATATGTGGCAAAAGAATCTTGAGATATTATTTTTCTCTTGATAATTTCTGTGATTTCTTTTCAACTCT
ATCCCCAATCAGAAAAGGTCCTTCTGGGCCAAAAATGAAGAGGTAGATTTATGCCAGTTAAGGTGTGGATC
ATGGAAGAGGACCCATGGGTATGACTAGT

The following amino acid sequence <SEQ ID NO.210> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.100:
TSHTHGSSSMIHTLTGINLPLHFWPRRTFSDWGSKEITEIIKRKIISQDSFATYLALKLRFSEHCILPQTT
HTHTHIEYFKIRNWATYNSGKRHLNGTEHHIYESSVQRISENVHKVSAFHRLGIEAVAITIKIQAQGKMKL
GVKGSEIHFRKAFKARKMRSTWYVF

The following DNA sequence nGPCR-2131 <SEQ ID NO.101> was identified in *H. sapiens*:
AGCACATAAGGATTTTTTTCCATGCCCCTATGATTTCATTTCCAACCAATCAGCAGCATTCACTGCCTAGC
CTCCTACCCATGAAATTGTACATAAAAACCCTGAGCTCAAAGCCTTTGGGAAGACTGATTTGAGTAAAATG
CCTGATTCTCCTGTGTGGCCAGTCTCGTGTCAATTAAACTCTCTACTACAATGCCATGGTGTCAATGCATC

TTGTCTGTGCAGTGCGCAGAAAGAACCCACTGGCAATTACATTACCAGTAGCTATCGCTCTTCTGTCCTTC
AAACAGGAAATACTTCAACCCTGGTAAGTCAATTAGGGTTTCTCATTCATTTGCGGAGCTCCTGGTGGCCT
GGCCTGAGACTCTCTCTGCGGCTCCTGTAACTCAGTGGCCCTTTTCATTCTCAGAAACATTTTTCCTGAAC
CTGTGTGTTCCCTGCCTCAATCTGTATTGGCTAATTTCTAGGCCTGTTAAATAACTGTCAATCTTGACCCC
ATCATAATTACCATCTAGAAATGCCATTTGTCTCTCATTTTTGTCATATCTCCTGCTTCCTGGATTCTGGG
AAGTTTATGCTTTGGGTGACAAATATCCATCTGAGAAAAAAAATACATGAAACTTCTTTAAATTCTTTACT
CCATAATA

The following amino acid sequence <SEQ ID NO.211> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.101:
STGFFSMPLFHFQPISSIHCLASYPNCTKPAQSLWEDFENAFSCVASLVSIKLSTTMPWCQCILSVQCAER
THWQLHYQLSLFCPSNRKYFNPGKSIRVSHSFAELLVAWPETLSAAPVTQWPFSFSETFFLNLCVPCLNLY
WLISRPVKLSILTPSLPSRNAICLSFLSYLLLPGFWEVYALGDKYPSEKKNTNFFKFFTP

The following DNA sequence nGPCR-2132 <SEQ ID NO.102> was identified in *H. sapiens*:
TTTATTGAAATAACTTATAGGAAATGACTTAAGTAATATAAAACACATCACACATTTTATCTGTATGTTGA
ATATCAAAATTGAGATTCCTAGAAAATTCTTATTTTCAAAAGTATATACCCAGATTACTTGTAAGCATTGG
AAAGACAATGGCTAATCACTCACATTTTGGAAATGAAAGAAATTACCTCAATCAGGACAAGTTCTTAGTGT
CACTCATTTAGTGGTAGATCCATGATAGAGAATGCAATTCTCAGACCAAAGATTATGGTTGGTTCCTTAAC
TATGCCTTGAATATACTAAACAACTTCCCATTTATCAGCTGGAGAACTTACAATGTTATAGGAGTGGTCAT
GGGCTTAAGAAAATGTTTACAGAGAGGTTATATATTGTATTAGAAAGCTGTTTATCAGGCCATGAATGTGC
TATCCACAGAGAAACTATGTTTTGTGGATATGGAAGGAAAGGAGTAAATAAGGCAAATGCATTG

The following amino acid sequence <SEQ ID NO.212> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.102:
MHLPYLLLSFPYPQNIVSLWIAHSWPDKQLSNTIYNLSVNIFLSPPLLHCKFSSMGSCLVYSRHSGTNHNL
WSENCILYHGSTTKVTLRTCPDGNFFHFQNVSDPLSFQCLQVIWVYTFENKNFLGISILIFNIQIKCVMCF
ILLKSFPISYFNK

The following DNA sequence nGPCR-2133 <SEQ ID NO.103> was identified in *H. sapiens*:
ACATGTTCAGTCAATTTTAAAATGTAACAAAAGAAAATGAATTATTATTAAATTACTAACTACTTTGTTTT
AGGCACTGAGCTAAGTAGTTGCTTTTGTTTAAATTCCTTTTAAAAGGTCGCACTAGCCTTGGTCTAAATAC
TAAGCTTCAAAGACTGAATGGGAATACTATTGAGTACATGCATCTAGTTCTCAGTATCTTCTTCCTTTCTG
ATCCTTTAGCAGGTCCAGACCAAGCAAGTCTGGTGGGGAGGAGCCTGTTCTAGATCTGGAGAGTCCCTGCA
TCCAATTCCAATTGGGTACTAAGTTCACTATTAGGGTGACAGGTTCAATAGAAACCCAAACGTCAGCATCA
CATAATATATCCATGTAACAAACCTGCACATGTGCCCTAGAATCTAAAATTAAATAAATAAATAAATAAAT
AAAGCAGTGGACCTGGGATAGGCCATGAATATCTACTATTTTAGATGAAGGATTAGGACAGTCCATGGATA
CAGTGCTTTCTTAAATAGACCCTCAAAATTCTGCATCATAAAATCCTGATACTCAGGAGCAATTTGAAGCA
CTCCATTTGGTACTGGAGTGTTTTTGAGTTGCTTTG

The following amino acid sequence <SEQ ID NO.213> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.103:
KATQKHSSTKWSASNCSVSGFYDAEFGSIESTVSMDCPNPSSKIVDIHGLSQVHCFIYLFIYLILDSRAHV
QVCYMDILCDADVWVSIEPVTLIVNLVPNWNWMQGLSRSRTGSSPPDLLGLDLLKDQKGRRYELDACTQYS
HSVFEAYLDQGCDLLKGITKATTLSANKVVSNLIIIHFLLLHFKIDTC

The following DNA sequence nGPCR-2134 <SEQ ID NO.104> was identified in *H. sapiens*:
ATGATTTTGGGATTTAAATATTACCACGGATCCCTTCTTCCTTCTTGAGTTTTTCTAAGGAGTGATAGACT
GGAAACAGTAACCATACTGAAAGTGAAATTTCTGGATCCATGAGGGTTTGGCACAACCCAATGGAGAAATC
TGGGAAAAGCTGAATTGGAAAAGTGGTGTGAGACTGGGAGGTTCCGGGTAGGCTTTGGCTCTTACTTCTAA
GTCTGAGTCGATAGGTGTG

The following amino acid sequence <SEQ ID NO.214> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.104:
TPIDSDLEVRAKAYPEPPSLTPLFQFSFSQISPLGCAKPSWIQKFHFQYGYCFQSITPKNSRRKKGSVVIF
KSQNH

The following DNA sequence nGPCR-2135 <SEQ ID NO.105> was identified in *H. sapiens*:
TTAGGGATACAGCCATTCATGGTGTTTTCATGAACTTATCCCTTATGAATGCATATGATATGTTCATTCAC
CTCTTTGTAGAAAGCTTTGATCGTTTTGCACAAAACAGGGAAGTAGTAGTAGTGGCAGTATGGATTTGGGA



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GGGTGAAGTTAGCTTTGGCCAGGTGATCTCTGCATATCAGACTATTAAAGGCAGCGCCTTTACAGAATGTT
GGCTGGGCTGTGACTCATGCTTTGCTTTGCACTCCCTAAAGAGGCTTTATGTATCGCCTCTTTGTCCTTTC
CCAAGTCATTTGAAAATAAATAGAAGAGAGAATAATGTGATCAGGGGCTCTAATTGTATTTATTGCTTATG
TAGGGTTGTAGTAGATACAGGGATGTTTCCTTATTCTTTATGTCTTGCACATCTGAAATGTGTCATAATAA
ATGATATTTTAAAAAACTAAACAGAACAACTAGTTTTGGGAATTTGTCCTACATAGTCATATGACTCATCT
G

The following amino acid sequence <SEQ ID NO.215> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.105:
RDTAIHGVFMNLSLMNAYDMFIHLFVESFDRFAQNREVVVVAVWIWEGEVSFGQVISAYQTIKGSAFTECW
LGCDSCFALHSLKRLYVSPLCPFPSHLKINRRFNNVIRGSNCIYCLCRVVVDTGMFPYSLCLAHLKCVIIN
DILKNTEQLVLGICPTSYDSSAILISL

The following DNA sequence nGPCR-2136 <SEQ ID NO.106> was identified in *H. sapiens*:
TCTTCCCTTGTTTTATCTTATATCAAACTCTATAAGGAATAGGATCACACAGCTCCTAATAAGGAGGAGCA
TAAGGTAAAATCATGCACAGCATTTTAGTTAGAAAATATTAATCTTTATGTTTTCATTTCTTAGTCTTTTA
AATAATAAAAATGCATCGAAATGTTTAAAACTTTAAATATTGTAAAAGTTATAGTAAGACACGTTGCCAAC
TAGATTCATGCATCTAATTTCCTGAATTATAGTTAATAGTTTCATATTATAAACTCTTGATAAAAGTAATA
AATACATGGCAGATACACACATGCACATTTGTATTATATAATAGTAGTCCAGTGAACGCTTC

The following amino acid sequence <SEQ ID NO.216> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.106:
KRSLDYYYIIQMCMCVSAMYLLLLSRVYNMKLLTIIQEIRCMNLVGNVSYYNFYNISFKHFDAFLLFKRL
RNENIKINIFLKCCAFYLMLLLIRSCVILFLIEFDIRNKGR

The following DNA sequence nGPCR-2137 <SEQ ID NO.107> was identified in *H. sapiens*:
CTCACATATTACCTTCAAAGAAACCTGTCCTAATAAAAGCCATTCCTACTCTACTTGGCCTCCAGGATTTA
ACCACTTCCTACATTCAACCATCCTGGGACCTAGCTTTACTAGACTTCAATTTTGACCTTATTTATCTTGC
CTTTTGTCATAATTGCTTCTTGCTTTCGTGCTCCATTAAACACTAAGGTTTTTGAGAGCAGGAACTCAAAA
CACTTTAAATTCCTCTCTCTTCATATGCAGTTGCTTTTGCACAGTCAATACACAGTAAATGCTGATTGAAT
TGAAAGGATCTCACTCTTAGAATGCAATTCTCTCAGAGTCTCCAACTAGTCTAGTAGCTTAAAGACCAATC
CTACTTAAAAATTAACTTGAATTGTAAGTACAACAAAATCACTCCAAGTTATTAACCTAACCATTGAAGTG
TTTATTTTCCTACTTGGAAAACCAGGTCAACCACAGGGACCAACCTACCCTGGATAGGTGACTCTAAAAGT
AATGAGGTAATTTCCTTCAAAAATGACAAAGCTTTCAGGATTCTCTGGAATGCATACCCATTAATGTGTCA
CCATTAATCA

The following amino acid sequence <SEQ ID NO.217> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.107:
LTYYLQRNLSKPFLLYLASRIPLPTFNHPGTLYTSILTLFILPFVIIASCFRAPLNTKVFESRNSKHFKFL
SLHMQLLLHSQYTVNADIERISLLECNSLRVSNSSSLKTNPTKLTIVSTTKSLQVINLTIEVFIFLLGKPG
QPQGPTYPGVTLKVMRFPSKMTKLSGFSGMHTHCVTIN

The following DNA sequence nGPCR-2138 <SEQ ID NO.108> was identified in *H. sapiens*:
GGGCAAGGGTGATGGAGGTTTGAGGAGACAGGAGAAAGTGGGAAAAGTAGTTCGAATCAATGAATTCATTT
TTGGAATACAGTAGGATTACCAGGTTTGTGCTCATAATTTAAAGTGAGACCAGTCAACAGTGTTGCAATTT
CCTTATAGCCATTTCAGCTACTCAAGCCCATGTGTGGAATAAACAGACAGTCTGATTCAACTAGGGACGGA
GTTTGCCCGAGGGCATAACCACTAAACAGAAGAAAAAAGGAGAAAGGGAGGGGTGACTGCACTCAAAAAAT
ACAATAAGTAGGTATTTACCTGGCTTACGTTCTAAAAGCTGCTGTAAATGAAACACTGCTTGTTCATAGTC
TTGTTTTCTGAACATGAGATCAGCCATCATCTATAAAGATAAAAGTTGGTTCTAAAAATATTGCCATGTAT
TTTACACAACATGTTCTTCCAATCAAGATTTAGCACTAGAAAAATATAGATGATAAACATGAGGAGGGGGC
AGCATTTTATAAAAAGGAGGCATTTAAGATTCAAGCCCACCTTGTGCAGAATAACTTGCAGATCAGTGTAA
CAGAAGATAATCAAGGATGTGAAACAGATTGCTCTGCTTGCAAAATTGTATTTTTAGCAAAAAATATGTTT
CTAGCAATTGTTTTAAAAACAGAAATTTGAAGGAATTGCACACTCTATGTGCT

The following amino acid sequence <SEQ ID NO.218> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.108:
HIECAIPSNFCFNNCKHIFCKYNFASRAICFTSLIIFCYTDLQVILHKVGLNLKCLLFIKCCPLLMFIIYI
FLVLNLDWKNMLCKIHGNIFRTNFYLYRWLISCSENKTMNKQCFIYSSFNVSQVNTYLLYFLSAVTPPFLL
FSSVWLCPRANSVPSIRLSVYSTHGLELKWLGNCNTVDWSHFKLAQTWSYCIPKMNSLIRTTFPTFSCLLK
PPSPLP

The following DNA sequence nGPCR-2139 <SEQ ID NO.109> was identified in



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H. sapiens:
ACTTTGTCCTATGCATCTTTTCCCTTGGTTAATCTGTGTCTGTATCCTCTCCCTGTAATAAACTGTAATCG
ACTTTGTCCTATGCATCTTTTCCCTTGGTTAATCTGTGTCTGTATCCTCTCCCTGTAATAAACTGTAATCG
CAAGTGAGCTGCTTTCAGTGAGTTTTTTGAGTGTTCCTAGTAAATTATCAAACCTGAAGGGGATTTGGGGA
ACTCCTTGAATTTGCAATTGGTGTTAGGAGTGAAGACAATCTTGTGTGTACCGTGTTCTCTCTAACTTTAT
GGGGTTTAGGCATGGTGGGTGGTAGAGAATGAAGTAGGTGTGTAAAATTAACTGTGATCTGATTCTTACCT
AAAAAAAAACTTTCCCCATAGCAGGGCTGATATAAAGAAGCCACAACTTAGGTTTTTCCTACTTTGCACAC
AAAATTCCAACAGTGGAACTTCTGAATGATTTACTTAGGAAATTACATATGGAGAAATGTTTTGAAACTAC
AAATTCTCACCAAAGATTTCCTAAAATACTCCAATAAGGTGATAGACTGTAATCAGAACTCACATTTACCA
AAAAGGAGATGGTATTCTATTTTGAAAGTAATTATATTACTGGGAAAACAATGTTTACCAGTTTTAATTAT
AATACTGGAAACAACAGTTTTTATAAATGTTTCTGAATGAATTTACAATTTAAATGAATAAATCCTTATGC
CTAAAATGAACACTGGGCACATTTTTAAGCACTAC

The following amino acid sequence <SEQ ID NO.219> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.109:
GLGMV
FVLCIFSLGSVSVSSPCNKLSQVSCFQVFVFLVNYQTRGFGELLEFAIGVRSEDNLVCTVFSLTLW
GGRESRCVKLTVIFLPKKKLSPQGYKEATTVFPTLHTKFQQWNFMIYLGNYIWRNVLKLQILTKDFLKYSN
KVIDCNQNSHLPKRRWYSILKVIILLGKQCLPVLIIILETTVFINVSEIYNLNEILMPKMNTGHIFKHY

The following DNA sequence nGPCR-2140 <SEQ ID NO.110> was identified in H. sapiens:
TATACTTAAGATTATTTCTTTGGACACTGTTCTGTTATAGTAATGTGTCTGATCCTACAGAAGTACCATAG
TATTTTAATCATTATAATTTCCAATATAAGTTATACGTGATAGATCAAGTTCTTTATAATTTTTTCTTCTT
CAGAGTTTTATCTGGAATTTATTCTGGTGTTTGATATGACATAAATATCTAATTTGTCTCCCAAACAGAGT
CAAGATGATTCCTGTAATGTTACTAATTTGTGTTCTGAGAAGGAAGAAAAGTGGCAGCACTATGGCACTGG
GAATTCTGCATAAACCCATGAAAGCAGTCACCTTTGTGAACGTGTTTTTGGTGGAAACAAGTGTTGAGAAC
CATTGTTGTATAATAGTGCTGTCCAGTAGAACTTACTCTGGTGATGGGAATACTCTATAGCTGTACTTTCC
AATATGGTATTCACTGACCACATGTGGCTATCAAGTACTTGAAATGTGGCTAGGTGACTGAGGAACCGAAA
TTTTTAGTCTTATTTAATTGTAATCAGTTTAAATTTATACAACTGCATATTTTATTGAATAGAGCACTTTC
TAGAGCATAGC

The following amino acid sequence <SEQ ID NO.220> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.110:
LICLPNRVKMIPVMLL
ILKIISLDTVLLCVSYRSTIVFSLFPIVIRDRSSSLFFLLQSFIWNLFWCLIHKY
ICVLRRKKSGSTMALGILHKPMKAVTFVNVFLVETSVENHCCIIVLSSRTYSGDGNTLLYFPIWYSLTTCG
YQVLEMWLGDGTEIFSLILSVIYTTAYFIESTFSI

## EXAMPLE 2: CLONING OF nGPCR-x

cDNAs may be sequenced directly using an AB1377 or ABI373A fluorescence-based sequencer (Perkin Elmer/Applied Biosystems Division, PE/ABD, Foster City, CA) and the ABI PRISM Ready Dye-Deoxy Terminator kit with Taq FS polymerase. Each ABI cycle sequencing reaction contains about 0.5μg of plasmid DNA. Cycle-sequencing is performed using an initial denaturation at 98°C for 1 min, followed by 50 cycles: 98°C for 30 sec, annealing at 50°C for 30 sec, and extension at 60°C for 4 min. Temperature cycles and times are controlled by a Perkin-Elmer 9600 thermocycler. Extension products are purified using Centriflex gel filtration (Advanced Genetic Technologies Corp., Gaithersburg, MD). Each reaction product is loaded by pipette onto the column, which is then centrifuged in a swinging bucket centrifuge (Sorvall model RT6000B table top centrifuge) at 1500 x g for 4 min at room temperature. Column-purified samples are dried under vacuum for about 40 min and then dissolved in 5μl of a DNA loading solution (83% deionized formamide, 8.3 mM EDTA, and 1.6 mg/ml Blue Dextran). The samples are then heated to 90°C for three min and loaded into the gel



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sample wells for sequence analysis by the ABI377 sequencer. Sequence analysis is performed by importing ABI373A files into the Sequencher program (Gene Codes, Ann Arbor, MI). Generally, sequence reads of 700 bp are obtained. Potential sequencing errors are minimized by obtaining sequence information from both DNA strands and by re-sequencing difficult areas using primers at different locations until all sequencing ambiguities are removed.

To isolate a cDNA clone encoding full length nGPCR, a DNA fragment corresponding to a nucleotide sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110, or a portion thereof, can be used as a probe for hybridization screening of a phage cDNA library. The DNA fragment is amplified by the polymerase chain reaction (PCR) method. The PCR reaction mixture of 50μl contains polymerase mixture (0.2mM dNTPs, 1x PCR Buffer and 0.75μl Expand High Fidelity Polymerase (Roche Biochemicals)), 1μg of 3206491 plasmid, and 50pmoles of forward primer and 50pmoles of reverse primer. The primers are preferably 10 to 25 nucleotides in length and are determined by procedures well known to those skilled in the art. Amplification is performed in an Applied Biosystems PE2400 thermocycler, using the following program: 95°C for 15 seconds, 52°C for 30 seconds and 72°C for 90 seconds; repeated for 25 cycles. The amplified product is separated from the plasmid by agarose gel electrophoresis, and purified by Qiaquick gel extraction kit (Qiagen).

A lambda phage library containing cDNAs cloned into lambda ZAPII phage-vector is plated with E. coli XL-1 blue host, on 15 cm LB-agar plates at a density of 50,000 pfu per plate, and grown overnight at 37°C; (plated as described by Sambrook *et al.*, *supra*). Phage plaques are transferred to nylon membranes (Amersham Hybond NJ), denatured for 2 minutes in denaturation solution (0.5 M NaOH, 1.5 M NaCl), renatured for 5 minutes in renaturation solution (1 M Tris pH 7.5, 1.5 M NaCl), and washed briefly in 2xSSC (20x SSC: 3 M NaCl, 0.3 M Na-citrate). Filter membranes are dried and incubated at 80°C for 120 minutes to cross link the phage DNA to the membranes.

The membranes are hybridized with a DNA probe prepared as described above. A DNA fragment (25ng) is labeled with $\alpha$-$^{32}$P-dCTP (NEN) using Rediprime random priming (Amersham Pharmacia Biotech), according to the manufacturer's instructions. Labeled DNA is separated from unincorporated nucleotides by S200 spin columns (Amersham Pharmacia Biotech), denatured at 95°C for 5 minutes and kept on ice. The DNA-containing membranes (above) are pre-hybridized in 50ml ExpressHyb (Clontech) solution at 68°C for 90 minutes. Subsequently, the labeled DNA probe is added to the hybridization solution, and the probe is left to hybridize to the membranes at 68°C for 70 minutes. The membranes are washed five times in 2x SSC, 0.1% SDS at 42°C for 5 minutes each, and finally washed 30 minutes in 0.1x SSC, 0.2% SDS. Filters are exposed to Kodak XAR film (Eastman Kodak Company, Rochester,



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N.Y., USA) with an intensifying screen at −80°C for 16 hours. One positive colony is isolated from the plates, and re-plated with about 1000 pfu on a 15 cm LB plate. Plating, plaque lift to filters and hybridization are performed as described above. About four positive phage plaques are isolated form this secondary screening.

cDNA containing plasmids (pBluescript SK-) are rescued from the isolated phages by in vivo excision by culturing XL-1 blue cells co-infected with the isolated phages and with the Excision helper phage, as described by the manufacturer (Stratagene). XL-blue cells containing the plasmids are plated on LB plates and grown at 37°C for 16 hours. Colonies (18) from each plate are replated on LB plates and grown. One colony from each plate is stricken onto a nylon filter in an ordered array, and the filter is placed on a LB plate to raise the colonies. The filter is then hybridized with a labeled probe as described above. About three positive colonies are selected and grown up in LB medium. Plasmid DNA is isolated from the three clones by Qiagen Midi Kit (Qiagen) according to the manufacturer's instructions. The size of the insert is determined by digesting the plasmid with the restriction enzymes NotI and SalI, which establishes an insert size. The sequence of the entire insert is determined by automated sequencing on both strands of the plasmids.

## EXAMPLE 3: SUBCLONING OF THE CODING REGION OF nGPCR-X VIA PCR

Additional experiments may be conducted to subclone the coding region of nGPCR and place the isolated coding region into a useful vector. Two additional PCR primers are designed based on the coding region of nGPCR, corresponding to either end. To protect against exonucleolytic attack during subsequent exposure to enzymes, *e.g.*, Taq polymerase, primers are routinely synthesized with a protective run of nucleotides at the 5' end that were not necessarily complementary to the desired target.

PCR is performed in a 50µl reaction containing 34µl $H_2O$, 5 µl 10X TT buffer (140 mM ammonium sulfate, 0.1% gelatin, 0.6 M Tris-tricine, pH 8.4), 5µl 15mM $MgSO_4$, 2µl dNTP mixture (dGTP, dATP, dTTP, and dCTP, each at 10 mM), 3µl genomic phage DNA (0.25µg/µl), 0.3µl Primer 1 (1µg/µl), 0.3µl Primer 2 (1µg/µl), 0.4µl High Fidelity Taq polymerase (Boehringer Mannheim). The PCR reaction was started with 1 cycle of 94°C for 2 minutes; followed by 25 cycles at 94°C for 30 seconds, 55°C for 30 seconds, and 72°C for 1.3 minutes.

The contents from the PCR reaction are loaded onto a 2% agarose gel and fractionated. The DNA band of expected size is excised from the gel, placed in a GenElute Agarose spin column (Supelco) and spun for 10 minutes at maximum speed in a microfuge. The eluted DNA is precipitated with ethanol and resuspended in 6µl $H_2O$ for ligation.



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The PCR-amplified DNA fragment containing the coding region is cloned into pCR2.1 using a protocol standard in the art. In particular, the ligation reaction consists of 6μl of GPCR DNA, 1μl 10X ligation buffer, 2μl pCR2.1 (25ng/μl, Invitrogen), and 1μl T4 DNA ligase (Invitrogen). The reaction mixture is incubated overnight at 14°C and the reaction is then stopped by heating at 65°C for 10 minutes. Two microliters of the ligation reaction are transformed into One Shot cells (Invitrogen) and plated onto ampicillin plates. A single colony containing a recombinant pCR2.1 bearing an insert is used to inoculate a 5ml culture of LB medium. Plasmid DNA is purified using the Concert Rapid Plasmid Miniprep System (GibcoBRL) and sequenced. Following confirmation of the sequence, a 50 ml culture of LB medium is inoculated with the transformed One Shot cells, cultured, and processed using a Qiagen Plasmid Midi Kit to yield purified pCR-GPCR.

**EXAMPLE 4: HYBRIDIZATION ANALYSIS TO DEMONSTRATE nGPCR-X EXPRESSION IN BRAIN**

The expression of nGPCR-x in mammals, such as the rat, may be investigated by *in situ* hybridization histochemistry. To investigate expression in the brain, for example, coronal and sagittal rat brain cryosections (20μm thick) are prepared using a Reichert-Jung cryostat. Individual sections are thaw-mounted onto silanized, nuclease-free slides (CEL Associates, Inc., Houston, TX), and stored at -80°C. Sections are processed starting with post-fixation in cold 4% paraformaldehyde, rinsed in cold phosphate-buffered saline (PBS), acetylated using acetic anhydride in triethanolamine buffer, and dehydrated through a series of alcohol washes in 70%, 95%, and 100% alcohol at room temperature. Subsequently, sections are delipidated in chloroform, followed by rehydration through successive exposure to 100% and 95% alcohol at room temperature. Microscope slides containing processed cryosections are allowed to air dry prior to hybridization. Other tissues may be assayed in a similar fashion.

A nGPCR-x-specific probe is generated using PCR. Following PCR amplification, the fragment is digested with restriction enzymes and cloned into pBluescript II cleaved with the same enzymes. For production of a probe specific for the sense strand of nGPCR-x, the nGPCR-x clone in pBluescript II is linearized with a suitable restriction enzyme, which provides a substrate for labeled run-off transcripts (*i.e.*, cRNA riboprobes) using the vector-borne T7 promoter and commercially available T7 RNA polymerase. A probe specific for the antisense strand of nGPCR-x is also readily prepared using the nGPCR-x clone in pBluescript II by cleaving the recombinant plasmid with a suitable restriction enzyme to generate a linearized substrate for the production of labeled run-off cRNA transcripts using the T3 promoter and cognate polymerase. The riboprobes are labeled with [$^{35}$S]-UTP to yield a specific activity of



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about 0.40 x $10^6$ cpm/pmol for antisense riboprobes and about 0.65 x $10^6$ cpm/pmol for sense-strand riboprobes. Each riboprobe is subsequently denatured and added (2 pmol/ml) to hybridization buffer which contained 50% formamide, 10% dextran, 0.3 M NaCl, 10 mM Tris (pH 8.0), 1 mM EDTA, 1X Denhardt's Solution, and 10 mM dithiothreitol. Microscope slides containing sequential brain cryosections are independently exposed to 45 μl of hybridization solution per slide and silanized cover slips are placed over the sections being exposed to hybridization solution. Sections are incubated overnight (15-18 hours) at 52°C to allow hybridization to occur. Equivalent series of cryosections are exposed to sense or antisense nGPCR-x-specific cRNA riboprobes.

Following the hybridization period, coverslips are washed off the slides in 1X SSC, followed by RNase A treatment involving the exposure of slides to 20 μg/ml RNase A in a buffer containing 10mM Tris-HCl (pH 7.4), 0.5M EDTA, and 0.5M NaCl for 45 minutes at 37°C. The cryosections are then subjected to three high-stringency washes in 0.1 X SSC at 52°C for 20 minutes each. Following the series of washes, cryosections are dehydrated by consecutive exposure to 70%, 95%, and 100% ammonium acetate in alcohol, followed by air drying and exposure to Kodak BioMax™ MR-1 film. After 13 days of exposure, the film is developed. Based on these results, slides containing tissue that hybridized, as shown by film autoradiograms, are coated with Kodak NTB-2 nuclear track emulsion and the slides are stored in the dark for 32 days. The slides are then developed and counterstained with hematoxylin. Emulsion-coated sections are analyzed microscopically to determine the specificity of labeling. The signal is determined to be specific if autoradiographic grains (generated by antisense probe hybridization) are clearly associated with cresyl violate-stained cell bodies. Autoradiographic grains found between cell bodies indicates non-specific binding of the probe.

As discussed above, it is well known that GPCRs are expressed in many different tissues and regions, including in the brain. Expression of nGPCR-x in the brain provides an indication that modulators of nGPCR-x activity have utility for treating neurological disorders, including but not limited to, mental disorder, affective disorders, ADHD/ADD (*i.e.*, Attention Deficit-Hyperactivity Disorder/Attention Deficit Disorder), and neural disorders such as Alzheimer's disease, Parkinson's disease, migraine, and senile dementia. Some other diseases for which modulators of nGPCR-x may have utility include depression, anxiety, bipolar disease, epilepsy, neuritis, neurasthenia, neuropathy, neuroses, and the like. Use of nGPCR-x modulators, including nGPCR-x ligands and anti-nGPCR-x antibodies, to treat individuals having such disease states is intended as an aspect of the invention.



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## EXAMPLE 5: TISSUE EXPRESSION PROFILING

A PCR-based system (RapidScan™ Gene Expression Panel, OriGene Technologies, Rockville, MD) may be used to generate a comprehensive expression profile of the putative nGPCR-x in human tissue, and in human brain regions. The RapidScan Expression Panel is comprised of first-strand cDNAs from various human tissues and brain regions that are serially diluted over a 4-log range and arrayed into a multi-well PCR plate. Human tissues in the array may include: brain, heart, kidney, spleen, liver, colon, lung, small intestine, muscle, stomach, testis, placenta, salivary gland, thyroid, adrenal gland, pancreas, ovary, uterus, prostate, skin, PBL, bone marrow, fetal brain, and fetal liver.

Expression of nGPCR-x in various tissues is detected using PCR primers designed based on the available sequence of the receptor that will prime the synthesis of a predetermined size fragment in the presence of the appropriate cDNA.

PCR is performed in a 50μl reaction containing 34μl $H_2O$, 5μl 10X TT buffer (140 mM ammonium sulfate, 0.1% gelatin, 0.6 M Tris-tricine, pH 8.4), 5μl 15mM $MgSO_4$, 2μl dNTP mixture (dGTP, dATP, dTTP, and dCTP, each at 10mM), 0.3μl forward primer (1μg/μl), 0.3μl reverse primer (1μg/μl), 0.4μl High Fidelity Taq polymerase (Boehringer Mannheim). The PCR reaction mixture is added to each well of the PCR plate. The plate is placed in a MJ Research PTC100 thermocycler, and is then exposed to the following cycling parameters: Pre-soak 94°C for 3 min; denaturation at 94°C for 30 seconds; annealing at primer 57°C for 45 seconds; extension 72°C for 2 minutes; for 35 cycles. PCR productions are then separated and analyzed by electrophoresis on a 1.2% agarose gel stained with ethidium bromide.

The 4-log dilution range of cDNA deposited on the plate ensures that the amplification reaction is within the linear range and, hence, facilitates semi-quantitative determination of relative mRNA accumulation in the various tissues or brain regions examined.

## EXAMPLE 6: NORTHERN BLOT ANALYSIS

Northern blots are performed to examine the expression of nGPCR-x mRNA. The sense orientation oligonucleotide and the antisense-orientation oligonucleotide, described above, are used as primers to amplify a portion of the GPCR-x cDNA sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110.

Multiple human tissue northern blots from Clontech (Human II # 7767-1) are hybridized with the probe. Pre-hybridization is carried out at 42 C for 4 hours in 5xSSC, 1X Denhardt's reagent, 0.1% SDS, 50% formamide, 250 mg/ml salmon sperm DNA. Hybridization is performed overnight at 42°C in the same mixture with the addition of about $1.5 \times 10^6$ cpm/ml of labeled probe.



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The probe is labeled with α-$^{32}$P-dCTP by Rediprime™ DNA labeling system (Amersham Pharmacia), purified on Nick Column™ (Amersham Pharmacia) and added to the hybridization solution. The filters are washed several times at 42°C in 0.2x SSC, 0.1% SDS. Filters are exposed to Kodak XAR film (Eastman Kodak Company, Rochester, N.Y., USA) with intensifying screen at –80°C.

**EXAMPLE 7: RECOMBINANT EXPRESSION OF nGPCR-X IN EUKARYOTIC HOST CELLS**

A. Expression of nGPCR-x in Mammalian Cells

To produce nGPCR-x protein, a nGPCR-x-encoding polynucleotide is expressed in a suitable host cell using a suitable expression vector and standard genetic engineering techniques. For example, the nGPCR-x-encoding sequence described in Example 1 is subcloned into the commercial expression vector pzeoSV2 (Invitrogen, San Diego, CA) and transfected into Chinese Hamster Ovary (CHO) cells using the transfection reagent FuGENE6™ (Boehringer-Mannheim) and the transfection protocol provided in the product insert. Other eukaryotic cell lines, including human embryonic kidney (HEK 293) and COS cells, are suitable as well. Cells stably expressing nGPCR-x are selected by growth in the presence of 100μg/ml zeocin (Stratagene, LaJolla, CA). Optionally, nGPCR-x may be purified from the cells using standard chromatographic techniques. To facilitate purification, antisera is raised against one or more synthetic peptide sequences that correspond to portions of the nGPCR-x amino acid sequence, and the antisera is used to affinity purify nGPCR-x. The nGPCR-x also may be expressed in-frame with a tag sequence (*e.g.*, polyhistidine, hemagluttinin, FLAG) to facilitate purification. Moreover, it will be appreciated that many of the uses for nGPCR-x polypeptides, such as assays described below, do not require purification of nGPCR-x from the host cell.

B. Expression of nGPCR-x in HEK-293 cells

For expression of nGPCR-x in mammalian cells HEK293 (transformed human, primary embryonic kidney cells), a plasmid bearing the relevant nGPCR-x coding sequence is prepared, using vector pSecTag2A (Invitrogen). Vector pSecTag2A contains the murine IgK chain leader sequence for secretion, the c-myc epitope for detection of the recombinant protein with the anti-myc antibody, a C-terminal polyhistidine for purification with nickel chelate chromatography, and a Zeocin resistant gene for selection of stable transfectants. The forward primer for amplification of this GPCR cDNA is determined by routine procedures and preferably contains a 5' extension of nucleotides to introduce the *HindIII* cloning site and nucleotides matching the GPCR sequence. The reverse primer is also determined by routine procedures and preferably contains a 5' extension of nucleotides to introduce an *XhoI* restriction site for cloning and



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nucleotides corresponding to the reverse complement of the nGPCR-x sequence. The PCR conditions are 55°C as the annealing temperature. The PCR product is gel purified and cloned into the *HindIII-XhoI* sites of the vector.

The DNA is purified using Qiagen chromatography columns and transfected into HEK-293 cells using DOTAP™ transfection media (Boehringer Mannheim, Indianapolis, IN). Transiently transfected cells are tested for expression after 24 hours of transfection, using western blots probed with anti-His and anti-nGPCR-x peptide antibodies. Permanently transfected cells are selected with Zeocin and propagated. Production of the recombinant protein is detected from both cells and media by western blots probed with anti-His, anti-Myc or anti-GPCR peptide antibodies.

C. Expression of nGPCR-x in COS cells

For expression of the nGPCR-x in COS7 cells, a polynucleotide molecule having a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110 can be cloned into vector p3-CI. This vector is a pUC18-derived plasmid that contains the HCMV (human cytomegalovirus) promoter-intron located upstream from the bGH (bovine growth hormone) polyadenylation sequence and a multiple cloning site. In addition, the plasmid contains the dhrf (dihydrofolate reductase) gene which provides selection in the presence of the drug methotrexane (MTX) for selection of stable transformants.

The forward primer is determined by routine procedures and preferably contains a 5' extension which introduces an *XbaI* restriction site for cloning, followed by nucleotides which correspond to a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110. The reverse primer is also determined by routine procedures and preferably contains 5'- extension of nucleotides which introduces a *SalI* cloning site followed by nucleotides which correspond to the reverse complement of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110. The PCR consists of an initial denaturation step of 5 min at 95°C 30 cycles of 30 sec denaturation at 95°C, 30 sec annealing at 58°C and 30 sec extension at 72°C, followed by 5 min extension at 72°C. The PCR product is gel purified and ligated into the *XbaI* and *SalI* sites of vector p3-CI. This construct is transformed into *E. coli* cells for amplification and DNA purification. The DNA is purified with Qiagen chromatography columns and transfected into COS 7 cells using Lipofectamine™ reagent from BRL, following the manufacturer's protocols. Forty-eight and 72 hours after transfection, the media and the cells are tested for recombinant protein expression.

nGPCR-x expressed from a COS cell culture can be purified by concentrating the cell-growth media to about 10 mg of protein/ml, and purifying the protein by, for example,



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chromatography. Purified nGPCR-x is concentrated to 0.5 mg/ml in an Amicon concentrator fitted with a YM-10 membrane and stored at -80°C.

D. Expression of nGPCR-x in Insect Cells

For expression of nGPCR-x in a baculovirus system, a polynucleotide molecule having a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110 can be amplified by PCR. The forward primer is determined by routine procedures and preferably contains a 5' extension which adds the *NdeI* cloning site, followed by nucleotides which correspond to a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110. The reverse primer is also determined by routine procedures and preferably contains a 5' extension which introduces the *KpnI* cloning site, followed by nucleotides which correspond to the reverse complement of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110.

The PCR product is gel purified, digested with *NdeI* and *KpnI*, and cloned into the corresponding sites of vector pACHTL-A (Pharmingen, San Diego, CA). The pAcHTL expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV), and a 6XHis tag upstream from the multiple cloning site. A protein kinase site for phosphorylation and a thrombin site for excision of the recombinant protein precede the multiple cloning site is also present. Of course, many other baculovirus vectors could be used in place of pAcHTL-A, such as pAc373, pVL941 and pAcIM1. Other suitable vectors for the expression of GPCR polypeptides can be used, provided that the vector construct includes appropriately located signals for transcription, translation, and trafficking, such as an in-frame AUG and a signal peptide, as required. Such vectors are described in Luckow *et al.*, Virology 170:31-39, among others.

The virus is grown and isolated using standard baculovirus expression methods, such as those described in Summers *et al.* (A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures, Texas Agricultural Experimental Station Bulletin No. 1555 (1987)).

In a preferred embodiment, pAcHLT-A containing nGPCR-x gene is introduced into baculovirus using the "BaculoGold™" transfection kit (Pharmingen, San Diego, CA) using methods established by the manufacturer. Individual virus isolates are analyzed for protein production by radiolabeling infected cells with $^{35}$S-methionine at 24 hours post infection. Infected cells are harvested at 48 hours post infection, and the labeled proteins are visualized by SDS-PAGE. Viruses exhibiting high expression levels can be isolated and used for scaled up expression.

For expression of a nGPCR-x polypeptide in a Sf9 cells, a polynucleotide molecule having a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110 can



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be amplified by PCR using the primers and methods described above for baculovirus expression. The nGPCR-x cDNA is cloned into vector pAcHLT-A (Pharmingen) for expression in Sf9 insect. The insert is cloned into the *NdeI* and *KpnI* sites, after elimination of an internal *NdeI* site (using the same primers described above for expression in baculovirus). DNA is purified with Qiagen chromatography columns and expressed in Sf9 cells. Preliminary Western blot experiments from non-purified plaques are tested for the presence of the recombinant protein of the expected size which reacted with the GPCR-specific antibody. These results are confirmed after further purification and expression optimization in HiG5 cells.

**EXAMPLE 8: INTERACTION TRAP/TWO-HYBRID SYSTEM**

In order to assay for nGPCR-x-interacting proteins, the interaction trap/two-hybrid library screening method can be used. This assay was first described in Fields *et al.*, *Nature,* **1989**, *340*, 245, which is incorporated herein by reference in its entirety. A protocol is published in Current Protocols in Molecular Biology 1999, John Wiley & Sons, NY, and Ausubel, F. M. *et al.* 1992, Short protocols in molecular biology, Fourth edition, Greene and Wiley-interscience, NY, each of which is incorporated herein by reference in its entirety. Kits are available from Clontech, Palo Alto, CA (Matchmaker Two-Hybrid System 3).

A fusion of the nucleotide sequences encoding all or partial nGPCR-x and the yeast transcription factor GAL4 DNA-binding domain (DNA-BD) is constructed in an appropriate plasmid (*i.e.*, pGBKT7) using standard subcloning techniques. Similarly, a GAL4 active domain (AD) fusion library is constructed in a second plasmid (*i.e.*, pGADT7) from cDNA of potential GPCR-binding proteins (for protocols on forming cDNA libraries, see Sambrook *et al.* 1989, Molecular cloning: a laboratory manual, second edition, Cold Spring Harbor Press, Cold Spring Harbor, NY), which is incorporated herein by reference in its entirety. The DNA-BD/nGPCR-x fusion construct is verified by sequencing, and tested for autonomous reporter gene activation and cell toxicity, both of which would prevent a successful two-hybrid analysis. Similar controls are performed with the AD/library fusion construct to ensure expression in host cells and lack of transcriptional activity. Yeast cells are transformed (*ca.* 105 transformants/mg DNA) with both the nGPCR-x and library fusion plasmids according to standard procedures (Ausubel *et al.*, 1992, Short protocols in molecular biology, fourth edition, Greene and Wiley-interscience, NY, which is incorporated herein by reference in its entirety). *In vivo* binding of DNA-BD/nGPCR-x with AD/library proteins results in transcription of specific yeast plasmid reporter genes (*i.e.*, lacZ, HIS3, ADE2, LEU2). Yeast cells are plated on nutrient-deficient media to screen for expression of reporter genes. Colonies are dually assayed for β-galactosidase activity upon growth in Xgal (5-bromo-4-chloro-3-indolyl-β-D-galactoside)



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supplemented media (filter assay for β-galactosidase activity is described in Breeden *et al.*, Cold Spring Harb. Symp. Quant. Biol., 1985, 50, 643, which is incorporated herein by reference in its entirety). Positive AD-library plasmids are rescued from transformants and reintroduced into the original yeast strain as well as other strains containing unrelated DNA-BD fusion proteins to confirm specific nGPCR-x/library protein interactions. Insert DNA is sequenced to verify the presence of an open reading frame fused to GAL4 AD and to determine the identity of the nGPCR-x-binding protein.

## EXAMPLE 9: MOBILITY SHIFT DNA-BINDING ASSAY USING GEL ELECTROPHORESIS

A gel electrophoresis mobility shift assay can rapidly detect specific protein-DNA interactions. Protocols are widely available in such manuals as Sambrook *et al.* **1989**, *Molecular cloning: a laboratory* manual, second edition, Cold Spring Harbor Press, Cold Spring Harbor, NY and Ausubel, F. M. *et al.*, 1992, Short Protocols in Molecular Biology, fourth edition, Greene and Wiley-interscience, NY, each of which is incorporated herein by reference in its entirety.

Probe DNA(<300 bp) is obtained from synthetic oligonucleotides, restriction endonuclease fragments, or PCR fragments and end-labeled with $^{32}P$. An aliquot of purified nGPCR-x (*ca.* 15 μg) or crude nGPCR-x extract (*ca.* 15 ng) is incubated at constant temperature (in the range 22-37 C) for at least 30 minutes in 10-15 μl of buffer (*i.e.* TAE or TBE, pH 8.0-8.5) containing radiolabeled probe DNA, nonspecific carrier DNA (*ca.* 1 μg), BSA (300 μg/ml), and 10% (v/v) glycerol. The reaction mixture is then loaded onto a polyacrylamide gel and run at 30-35 mA until good separation of free probe DNA from protein-DNA complexes occurs. The gel is then dried and bands corresponding to free DNA and protein-DNA complexes are detected by autoradiography.

## EXAMPLE 10: ANTIBODIES TO nGPCR-X

Standard techniques are employed to generate polyclonal or monoclonal antibodies to the nGPCR-x receptor, and to generate useful antigen-binding fragments thereof or variants thereof, including "humanized" variants. Such protocols can be found, for example, in Sambrook *et al.* (1989) and Harlow *et al.* (Eds.), Antibodies A Laboratory Manual; Cold Spring Harbor Laboratory; Cold Spring Harbor, NY (1988). In one embodiment, recombinant nGPCR-x polypeptides (or cells or cell membranes containing such polypeptides) are used as antigen to generate the antibodies. In another embodiment, one or more peptides having amino acid sequences corresponding to an immunogenic portion of nGPCR-x (*e.g.*, 6, 7, 8, 9, 10, 11, 12, 13,



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14, 15, 16, 17, 18, 19, 20, or more amino acids) are used as antigen. Peptides corresponding to extracellular portions of nGPCR-x, especially hydrophilic extracellular portions, are preferred. The antigen may be mixed with an adjuvant or linked to a hapten to increase antibody production.

A. Polyclonal or Monoclonal antibodies

As one exemplary protocol, recombinant nGPCR-x or a synthetic fragment thereof is used to immunize a mouse for generation of monoclonal antibodies (or larger mammal, such as a rabbit, for polyclonal antibodies). To increase antigenicity, peptides are conjugated to Keyhole Lympet Hemocyanin (Pierce), according to the manufacturer's recommendations. For an initial injection, the antigen is emulsified with Freund's Complete Adjuvant and injected subcutaneously. At intervals of two to three weeks, additional aliquots of nGPCR-x antigen are emulsified with Freund's Incomplete Adjuvant and injected subcutaneously. Prior to the final booster injection, a serum sample is taken from the immunized mice and assayed by western blot to confirm the presence of antibodies that immunoreact with nGPCR-x. Serum from the immunized animals may be used as polyclonal antisera or used to isolate polyclonal antibodies that recognize nGPCR-x. Alternatively, the mice are sacrificed and their spleen removed for generation of monoclonal antibodies.

To generate monoclonal antibodies, the spleens are placed in 10 ml serum-free RPMI 1640, and single cell suspensions are formed by grinding the spleens in serum-free RPMI 1640, supplemented with 2 mM L-glutamine, 1 mM sodium pyruvate, 100 units/ml penicillin, and 100 μg/ml streptomycin (RPMI) (Gibco, Canada). The cell suspensions are filtered and washed by centrifugation and resuspended in serum-free RPMI. Thymocytes taken from three naive Balb/c mice are prepared in a similar manner and used as a Feeder Layer. NS-1 myeloma cells, kept in log phase in RPMI with 10% fetal bovine serum (FBS) (Hyclone Laboratories, Inc., Logan, Utah) for three days prior to fusion, are centrifuged and washed as well.

To produce hybridoma fusions, spleen cells from the immunized mice are combined with NS-1 cells and centrifuged, and the supernatant is aspirated. The cell pellet is dislodged by tapping the tube, and 2 ml of 37°C PEG 1500 (50% in 75 mM HEPES, pH 8.0) (Boehringer-Mannheim) is stirred into the pellet, followed by the addition of serum-free RPMI. Thereafter, the cells are centrifuged, resuspended in RPMI containing 15% FBS, 100 μM sodium hypoxanthine, 0.4 μM aminopterin, 16 μM thymidine (HAT) (Gibco), 25 units/ml IL-6 (Boehringer-Mannheim) and 1.5 x $10^6$ thymocytes/ml, and plated into 10 Corning flat-bottom 96-well tissue culture plates (Corning, Corning New York).

On days 2, 4, and 6 after the fusion, 100μl of medium is removed from the wells of the fusion plates and replaced with fresh medium. On day 8, the fusions are screened by ELISA,



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testing for the presence of mouse IgG that binds to nGPCR-x. Selected fusion wells are further cloned by dilution until monoclonal cultures producing anti-nGPCR-x antibodies are obtained.

B. Humanization of anti-nGPCR-x monoclonal antibodies

The expression pattern of nGPCR-x as reported herein and the proven track record of GPCRs as targets for therapeutic intervention suggest therapeutic indications for nGPCR-x inhibitors (antagonists). nGPCR-x-neutralizing antibodies comprise one class of therapeutics useful as nGPCR-x antagonists. Following are protocols to improve the utility of anti-nGPCR-x monoclonal antibodies as therapeutics in humans by "humanizing" the monoclonal antibodies to improve their serum half-life and render them less immunogenic in human hosts (*i.e.*, to prevent human antibody response to non-human anti-nGPCR-x antibodies).

The principles of humanization have been described in the literature and are facilitated by the modular arrangement of antibody proteins. To minimize the possibility of binding complement, a humanized antibody of the IgG4 isotype is preferred.

For example, a level of humanization is achieved by generating chimeric antibodies comprising the variable domains of non-human antibody proteins of interest with the constant domains of human antibody molecules. (See, *e.g.*, Morrison *et al.*, Adv. Immunol., 44:65-92 (1989)). The variable domains of nGPCR-x-neutralizing anti-nGPCR-x antibodies are cloned from the genomic DNA of a B-cell hybridoma or from cDNA generated from mRNA isolated from the hybridoma of interest. The V region gene fragments are linked to exons encoding human antibody constant domains, and the resultant construct is expressed in suitable mammalian host cells (*e.g.*, myeloma or CHO cells).

To achieve an even greater level of humanization, only those portions of the variable region gene fragments that encode antigen-binding complementarity determining regions ("CDR") of the non-human monoclonal antibody genes are cloned into human antibody sequences. (See, *e.g.*, Jones *et al.*, Nature 321:522-525 (1986); Riechmann *et al.*, Nature 332:323-327 (1988); Verhoeyen *et al.*, Science 239:1534-36 (1988); and Tempest *et al.*, Bio/Technology 9: 266-71 (1991)). If necessary, the β-sheet framework of the human antibody surrounding the CDR3 regions also is modified to more closely mirror the three dimensional structure of the antigen-binding domain of the original monoclonal antibody. (See Kettleborough *et al.*, Protein Engin., 4:773-783 (1991); and Foote *et al.*, J. Mol. Biol., 224:487-499 (1992)).

In an alternative approach, the surface of a non-human monoclonal antibody of interest is humanized by altering selected surface residues of the non-human antibody, *e.g.*, by site-directed mutagenesis, while retaining all of the interior and contacting residues of the non-human antibody. See Padlan, Molecular Immunol., 28(4/5):489-98 (1991).



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The foregoing approaches are employed using nGPCR-x-neutralizing anti-nGPCR-x monoclonal antibodies and the hybridomas that produce them to generate humanized nGPCR-x-neutralizing antibodies useful as therapeutics to treat or palliate conditions wherein nGPCR-x expression or ligand-mediated nGPCR-x signaling is detrimental.

C. Human nGPCR-x-Neutralizing Antibodies from Phage Display

Human nGPCR-x-neutralizing antibodies are generated by phage display techniques such as those described in Aujame *et al.*, Human Antibodies 8(4):155-168 (1997); Hoogenboom, TIBTECH 15:62-70 (1997); and Rader *et al.*, Curr. Opin. Biotechnol. 8:503-508 (1997), all of which are incorporated by reference. For example, antibody variable regions in the form of Fab fragments or linked single chain Fv fragments are fused to the amino terminus of filamentous phage minor coat protein pIII. Expression of the fusion protein and incorporation thereof into the mature phage coat results in phage particles that present an antibody on their surface and contain the genetic material encoding the antibody. A phage library comprising such constructs is expressed in bacteria, and the library is screened for nGPCR-x-specific phage-antibodies using labeled or immobilized nGPCR-x as antigen-probe.

D. Human nGPCR-x-neutralizing antibodies from transgenic mice

Human nGPCR-x-neutralizing antibodies are generated in transgenic mice essentially as described in Bruggemann *et al.*, Immunol. Today 17(8):391-97 (1996) and Bruggemann *et al.*, Curr. Opin. Biotechnol. 8:455-58 (1997). Transgenic mice carrying human V-gene segments in germline configuration and that express these transgenes in their lymphoid tissue are immunized with a nGPCR-x composition using conventional immunization protocols. Hybridomas are generated using B cells from the immunized mice using conventional protocols and screened to identify hybridomas secreting anti-nGPCR-x human antibodies (*e.g.*, as described above).

**EXAMPLE 11: ASSAYS TO IDENTIFY MODULATORS OF nGPCR-X ACTIVITY**

Set forth below are several nonlimiting assays for identifying modulators (agonists and antagonists) of nGPCR-x activity. Among the modulators that can be identified by these assays are natural ligand compounds of the receptor; synthetic analogs and derivatives of natural ligands; antibodies, antibody fragments, and/or antibody-like compounds derived from natural antibodies or from antibody-like combinatorial libraries; and/or synthetic compounds identified by high-throughput screening of libraries; and the like. All modulators that bind nGPCR-x are useful for identifying nGPCR-x in tissue samples (*e.g.*, for diagnostic purposes, pathological purposes, and the like). Agonist and antagonist modulators are useful for up-regulating and down-regulating nGPCR-x activity, respectively, to treat disease states characterized by abnormal levels of nGPCR-x activity. The assays may be performed using single putative



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modulators, and/or may be performed using a known agonist in combination with candidate antagonists (or visa versa).

A. cAMP Assays

In one type of assay, levels of cyclic adenosine monophosphate (cAMP) are measured in nGPCR-x-transfected cells that have been exposed to candidate modulator compounds. Protocols for cAMP assays have been described in the literature. (See, *e.g.*, Sutherland *et al.*, Circulation 37: 279 (1968); Frandsen *et al.*, Life Sciences 18: 529-541 (1976); Dooley *et al.*, Journal of Pharmacology and Experimental Therapeutics 283 (2): 735-41 (1997); and George *et al.*, Journal of Biomolecular Screening 2 (4): 235-40 (1997)). An exemplary protocol for such an assay, using an Adenylyl Cyclase Activation FlashPlate® Assay from NEN™ Life Science Products, is set forth below.

Briefly, the nGPCR-x coding sequence (*e.g.*, a cDNA or intronless genomic DNA) is subcloned into a commercial expression vector, such as pzeoSV2 (Invitrogen), and transiently transfected into Chinese Hamster Ovary (CHO) cells using known methods, such as the transfection protocol provided by Boehringer-Mannheim when supplying the FuGENE 6 transfection reagent. Transfected CHO cells are seeded into 96-well microplates from the FlashPlate® assay kit, which are coated with solid scintillant to which antisera to cAMP has been bound. For a control, some wells are seeded with wild type (untransfected) CHO cells. Other wells in the plate receive various amounts of a cAMP standard solution for use in creating a standard curve.

One or more test compounds (*i.e.*, candidate modulators) are added to the cells in each well, with water and/or compound-free medium/diluent serving as a control or controls. After treatment, cAMP is allowed to accumulate in the cells for exactly 15 minutes at room temperature. The assay is terminated by the addition of lysis buffer containing [$^{125}$I]-labeled cAMP, and the plate is counted using a Packard Topcount™ 96-well microplate scintillation counter. Unlabeled cAMP from the lysed cells (or from standards) and fixed amounts of [$^{125}$I]-cAMP compete for antibody bound to the plate. A standard curve is constructed, and cAMP values for the unknowns are obtained by interpolation. Changes in intracellular cAMP levels of cells in response to exposure to a test compound are indicative of nGPCR-x modulating activity. Modulators that act as agonists of receptors which couple to the $G_s$ subtype of G proteins will stimulate production of cAMP, leading to a measurable 3-10 fold increase in cAMP levels. Agonists of receptors which couple to the $G_{i/o}$ subtype of G proteins will inhibit forskolin-stimulated cAMP production, leading to a measurable decrease in cAMP levels of 50-100%. Modulators that act as inverse agonists will reverse these effects at receptors that are either constitutively active or activated by known agonists.



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B. Aequorin Assays

In another assay, cells (*e.g.*, CHO cells) are transiently co-transfected with both a nGPCR-x expression construct and a construct that encodes the photoprotein apoaquorin. In the presence of the cofactor coelenterazine, apoaquorin will emit a measurable luminescence that is proportional to the amount of intracellular (cytoplasmic) free calcium. (See generally, Cobbold, *et al.* "Aequorin measurements of cytoplasmic free calcium," *In*: McCormack J.G. and Cobbold P.H., eds., *Cellular Calcium: A Practical Approach*. Oxford:IRL Press (1991); Stables *et al.*, Analytical Biochemistry 252: 115-26 (1997); and Haugland, Handbook of Fluorescent Probes and Research Chemicals. Sixth edition. Eugene OR: Molecular Probes (1996).)

In one exemplary assay, nGPCR-x is subcloned into the commercial expression vector pzeoSV2 (Invitrogen) and transiently co-transfected along with a construct that encodes the photoprotein apoaquorin (Molecular Probes, Eugene, OR) into CHO cells using the transfection reagent FuGENE 6 (Boehringer-Mannheim) and the transfection protocol provided in the product insert.

The cells are cultured for 24 hours at 37°C in MEM (Gibco/BRL, Gaithersburg, MD) supplemented with 10% fetal bovine serum, 2 mM glutamine, 10 U/ml penicillin and 10 μg/ml streptomycin, at which time the medium is changed to serum-free MEM containing 5 μM coelenterazine (Molecular Probes, Eugene, OR). Culturing is then continued for two additional hours at 37°C. Subsequently, cells are detached from the plate using VERSEN (Gibco/BRL), washed, and resuspended at 200,000 cells/ml in serum-free MEM.

Dilutions of candidate nGPCR-x modulator compounds are prepared in serum-free MEM and dispensed into wells of an opaque 96-well assay plate at 50 μl/well. Plates are then loaded onto an MLX microtiter plate luminometer (Dynex Technologies, Inc., Chantilly, VA). The instrument is programmed to dispense 50μl cell suspensions into each well, one well at a time, and immediately read luminescence for 15 seconds. Dose-response curves for the candidate modulators are constructed using the area under the curve for each light signal peak. Data are analyzed with SlideWrite, using the equation for a one-site ligand, and $EC_{50}$ values are obtained. Changes in luminescence caused by the compounds are considered indicative of modulatory activity. Modulators that act as agonists at receptors which couple to the $G_q$ subtype of G proteins give an increase in luminescence of up to 100 fold. Modulators that act as inverse agonists will reverse this effect at receptors that are either constitutively active or activated by known agonists.

C. Luciferase Reporter Gene Assay

The photoprotein luciferase provides another useful tool for assaying for modulators of nGPCR-x activity. Cells (*e.g.*, CHO cells or COS 7 cells) are transiently co-transfected with



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both a nGPCR-x expression construct (*e.g.*, nGPCR-x in pzeoSV2) and a reporter construct which includes a gene for the luciferase protein downstream from a transcription factor binding site, such as the cAMP-response element (CRE), AP-1, or NF-kappa B. Agonist binding to receptors coupled to the $G_s$ subtype of G proteins leads to increases in cAMP, thereby activating the CRE transcription factor and resulting in expression of the luciferase gene. Agonist binding to receptors coupled to the $G_q$ subtype of G protein leads to production of diacylglycerol that activates protein kinase C, which activates the AP-1 or NF-kappa B transcription factors, in turn resulting in expression of the luciferase gene. Expression levels of luciferase reflect the activation status of the signaling events. (See generally, George *et al.*, Journal of Biomolecular Screening 2(4): 235-240 (1997); and Stratowa *et al.*, Current Opinion in Biotechnology 6: 574-581 (1995)). Luciferase activity may be quantitatively measured using, *e.g.*, luciferase assay reagents that are commercially available from Promega (Madison, WI).

In one exemplary assay, CHO cells are plated in 24-well culture dishes at a density of 100,000 cells/well one day prior to transfection and cultured at 37°C in MEM (Gibco/BRL) supplemented with 10% fetal bovine serum, 2 mM glutamine, 10 U/ml penicillin and 10 µg/ml streptomycin. Cells are transiently co-transfected with both a nGPCR-x expression construct and a reporter construct containing the luciferase gene. The reporter plasmids CRE-luciferase, AP-1-luciferase and NF-kappaB-luciferase may be purchased from Stratagene (LaJolla, CA). Transfections are performed using the FuGENE 6 transfection reagent (Boehringer-Mannheim) according to the supplier's instructions. Cells transfected with the reporter construct alone are used as a control. Twenty-four hours after transfection, cells are washed once with PBS pre-warmed to 37°C. Serum-free MEM is then added to the cells either alone (control) or with one or more candidate modulators and the cells are incubated at 37°C for five hours. Thereafter, cells are washed once with ice-cold PBS and lysed by the addition of 100 µl of lysis buffer per well from the luciferase assay kit supplied by Promega. After incubation for 15 minutes at room temperature, 15 µl of the lysate is mixed with 50 µl of substrate solution (Promega) in an opaque-white, 96-well plate, and the luminescence is read immediately on a Wallace model 1450 MicroBeta scintillation and luminescence counter (Wallace Instruments, Gaithersburg, MD).

Differences in luminescence in the presence versus the absence of a candidate modulator compound are indicative of modulatory activity. Receptors that are either constitutively active or activated by agonists typically give a 3 to 20-fold stimulation of luminescence compared to cells transfected with the reporter gene alone. Modulators that act as inverse agonists will reverse this effect.

D. Intracellular calcium measurement using FLIPR



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Changes in intracellular calcium levels are another recognized indicator of G protein-coupled receptor activity, and such assays can be employed to screen for modulators of nGPCR-x activity. For example, CHO cells stably transfected with a nGPCR-x expression vector are plated at a density of $4 \times 10^4$ cells/well in Packard black-walled, 96-well plates specially designed to discriminate fluorescence signals emanating from the various wells on the plate. The cells are incubated for 60 minutes at 37°C in modified Dulbecco's PBS (D-PBS) containing 36 mg/L pyruvate and 1 g/L glucose with the addition of 1% fetal bovine serum and one of four calcium indicator dyes (Fluo-3™ AM, Fluo-4™ AM, Calcium Green™-1 AM, or Oregon Green™ 488 BAPTA-1 AM), each at a concentration of 4 μM. Plates are washed once with modified D-PBS without 1% fetal bovine serum and incubated for 10 minutes at 37°C to remove residual dye from the cellular membrane. In addition, a series of washes with modified D-PBS without 1% fetal bovine serum is performed immediately prior to activation of the calcium response.

A calcium response is initiated by the addition of one or more candidate receptor agonist compounds, calcium ionophore A23187 (10 μM; positive control), or ATP (4 μM; positive control). Fluorescence is measured by Molecular Device's FLIPR with an argon laser (excitation at 488 nm). (See, *e.g.*, Kuntzweiler *et al.*, Drug Development Research, 44(1):14-20 (1998)). The F-stop for the detector camera was set at 2.5 and the length of exposure was 0.4 milliseconds. Basal fluorescence of cells was measured for 20 seconds prior to addition of candidate agonist, ATP, or A23187, and the basal fluorescence level was subtracted from the response signal. The calcium signal is measured for approximately 200 seconds, taking readings every two seconds. Calcium ionophore A23187 and ATP increase the calcium signal 200% above baseline levels. In general, activated GPCRs increase the calcium signal approximately 10-15% above baseline signal.

E. <u>Mitogenesis Assay</u>

In a mitogenesis assay, the ability of candidate modulators to induce or inhibit nGPCR-x-mediated cell division is determined. (*See, e.g.*, Lajiness *et al.*, Journal of Pharmacology and Experimental Therapeutics 267(3): 1573-1581 (1993)). For example, CHO cells stably expressing nGPCR-x are seeded into 96-well plates at a density of 5000 cells/well and grown at 37°C in MEM with 10% fetal calf serum for 48 hours, at which time the cells are rinsed twice with serum-free MEM. After rinsing, 80μl of fresh MEM, or MEM containing a known mitogen, is added along with 20μl MEM containing varying concentrations of one or more candidate modulators or test compounds diluted in serum-free medium. As controls, some wells on each plate receive serum-free medium alone, and some receive medium containing 10% fetal



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bovine serum. Untransfected cells or cells transfected with vector alone also may serve as controls.

After culture for 16-18 hours, 1μ Ci of [$^3$H]-thymidine (2 Ci/mmol) is added to the wells and cells are incubated for an additional 2 hours at 37°C. The cells are trypsinized and collected on filter mats with a cell harvester (Tomtec); the filters are then counted in a Betaplate counter. The incorporation of [$^3$H]-thymidine in serum-free test wells is compared to the results achieved in cells stimulated with serum (positive control). Use of multiple concentrations of test compounds permits creation and analysis of dose-response curves using the non-linear, least squares fit equation: $A = B \times [C/ (D + C)] + G$ where A is the percent of serum stimulation; B is the maximal effect minus baseline; C is the $EC_{50}$; D is the concentration of the compound; and G is the maximal effect. Parameters B, C and G are determined by Simplex optimization.

Agonists that bind to the receptor are expected to increase [$^3$H]-thymidine incorporation into cells, showing up to 80% of the response to serum. Antagonists that bind to the receptor will inhibit the stimulation seen with a known agonist by up to 100%.

F. <u>[$^{35}$S]GTPγS Binding Assay</u>

Because G protein-coupled receptors signal through intracellular G proteins whose activity involves GTP binding and hydrolysis to yield bound GDP, measurement of binding of the non-hydrolyzable GTP analog [$^{35}$S]GTPγS in the presence and absence of candidate modulators provides another assay for modulator activity. (*See, e.g.*, Kowal *et al.*, Neuropharmacology 37:179-187 (1998).)

In one exemplary assay, cells stably transfected with a nGPCR-x expression vector are grown in 10 cm tissue culture dishes to subconfluence, rinsed once with 5 ml of ice-cold $Ca^{2+}/Mg^{2+}$-free phosphate-buffered saline, and scraped into 5 ml of the same buffer. Cells are pelleted by centrifugation (500 x *g*, 5 minutes), resuspended in TEE buffer (25 mM Tris, pH 7.5, 5 mM EDTA, 5 mM EGTA), and frozen in liquid nitrogen. After thawing, the cells are homogenized using a Dounce homogenizer (one ml TEE per plate of cells), and centrifuged at 1,000 x *g* for 5 minutes to remove nuclei and unbroken cells.

The homogenate supernatant is centrifuged at 20,000 x *g* for 20 minutes to isolate the membrane fraction, and the membrane pellet is washed once with TEE and resuspended in binding buffer (20 mM HEPES, pH 7.5, 150 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA). The resuspended membranes can be frozen in liquid nitrogen and stored at -70°C until use.

Aliquots of cell membranes prepared as described above and stored at -70°C are thawed, homogenized, and diluted into buffer containing 20 mM HEPES, 10 mM $MgCl_2$, 1 mM EDTA, 120 mM NaCl, 10 μM GDP, and 0.2 mM ascorbate, at a concentration of 10-50 μg/ml. In a final volume of 90 μl, homogenates are incubated with varying concentrations of candidate



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modulator compounds or 100 μM GTP for 30 minutes at 30°C and then placed on ice. To each sample, 10 μl guanosine 5'-O-(3[$^{35}$S]thio) triphosphate (NEN, 1200 Ci/mmol; [$^{35}$S]-GTPγS), was added to a final concentration of 100-200 pM. Samples are incubated at 30°C for an additional 30 minutes, 1 ml of 10mM HEPES, pH 7.4, 10 mM $MgCl_2$, at 4°C is added and the reaction is stopped by filtration.

Samples are filtered over Whatman GF/B filters and the filters are washed with 20 ml ice-cold 10 mM HEPES, pH 7.4, 10 mM $MgCl_2$. Filters are counted by liquid scintillation spectroscopy. Nonspecific binding of [$^{35}$S]-GTPγS is measured in the presence of 100 μM GTP and subtracted from the total. Compounds are selected that modulate the amount of [$^{35}$S]-GTPγS binding in the cells, compared to untransfected control cells. Activation of receptors by agonists gives up to a five-fold increase in [$^{35}$S]GTPγS binding. This response is blocked by antagonists.

G. MAP Kinase Activity Assay

Evaluation of MAP kinase activity in cells expressing a GPCR provides another assay to identify modulators of GPCR activity. (See, *e.g.*, Lajiness *et al.*, Journal of Pharmacology and Experimental Therapeutics 267(3):1573-1581 (1993) and Boulton *et al.*, Cell 65:663-675 (1991).)

In one embodiment, CHO cells stably transfected with nGPCR-x are seeded into 6-well plates at a density of 70,000 cells/well 48 hours prior to the assay. During this 48-hour period, the cells are cultured at 37°C in MEM medium supplemented with 10% fetal bovine serum, 2mM glutamine, 10 U/ml penicillin and 10μg/ml streptomycin. The cells are serum-starved for 1-2 hours prior to the addition of stimulants.

For the assay, the cells are treated with medium alone or medium containing either a candidate agonist or 200 nM Phorbol ester- myristoyl acetate (*i.e.*, PMA, a positive control), and the cells are incubated at 37°C for varying times. To stop the reaction, the plates are placed on ice, the medium is aspirated, and the cells are rinsed with 1 ml of ice-cold PBS containing 1mM EDTA. Thereafter, 200μl of cell lysis buffer (12.5 mM MOPS, pH 7.3, 12.5 mM glycerophosphate, 7.5mM $MgCl_2$, 0.5mM EGTA, 0.5 mM sodium vanadate, 1mM benzamidine, 1mM dithiothreitol, 10 μg/ml leupeptin, 10 μg/ml aprotinin, 2μg/ml pepstatin A, and 1μM okadaic acid) is added to the cells. The cells are scraped from the plates and homogenized by 10 passages through a 23 3/4 G needle, and the cytosol fraction is prepared by centrifugation at 20,000 x *g* for 15 minutes.

Aliquots (5-10 μl containing 1-5 μg protein) of cytosol are mixed with 1 mM MAPK Substrate Peptide (APRTPGGRR (SEQ ID NO: 28), Upstate Biotechnology, Inc., N.Y.) and 50μM [γ-$^{32}$P]ATP (NEN, 3000 Ci/mmol), diluted to a final specific activity of ~2000 cpm/pmol,



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in a total volume of 25 μl. The samples are incubated for 5 minutes at 30°C, and reactions are stopped by spotting 20 μl on 2 $cm^2$ squares of Whatman P81 phosphocellulose paper. The filter squares are washed in 4 changes of 1% $H_3PO_4$, and the squares are subjected to liquid scintillation spectroscopy to quantitate bound label. Equivalent cytosolic extracts are incubated without MAPK substrate peptide, and the bound label from these samples are subtracted from the matched samples with the substrate peptide. The cytosolic extract from each well is used as a separate point. Protein concentrations are determined by a dye binding protein assay (Bio-Rad Laboratories). Agonist activation of the receptor is expected to result in up to a five-fold increase in MAPK enzyme activity. This increase is blocked by antagonists.

H. [$^3$H]Arachidonic Acid Release

The activation of GPCRs also has been observed to potentiate arachidonic acid release in cells, providing yet another useful assay for modulators of GPCR activity. (*See, e.g.*, Kanterman *et al.*, Molecular Pharmacology 39:364-369 (1991).) For example, CHO cells that are stably transfected with a nGPCR-x expression vector are plated in 24-well plates at a density of 15,000 cells/well and grown in MEM medium supplemented with 10% fetal bovine serum, 2 mM glutamine, 10 U/ml penicillin and 10 μg/ml streptomycin for 48 hours at 37°C before use. Cells of each well are labeled by incubation with [$^3$H]-arachidonic acid (Amersham Corp., 210 Ci/mmol) at 0.5 μCi/ml in 1 ml MEM supplemented with 10mM HEPES, pH 7.5, and 0.5% fatty-acid-free bovine serum albumin for 2 hours at 37°C. The cells are then washed twice with 1 ml of the same buffer.

Candidate modulator compounds are added in 1 ml of the same buffer, either alone or with 10μM ATP and the cells are incubated at 37°C for 30 minutes. Buffer alone and mock-transfected cells are used as controls. Samples (0.5 ml) from each well are counted by liquid scintillation spectroscopy. Agonists which activate the receptor will lead to potentiation of the ATP-stimulated release of [$^3$H]-arachidonic acid. This potentiation is blocked by antagonists.

I. Extracellular Acidification Rate

In yet another assay, the effects of candidate modulators of nGPCR-x activity are assayed by monitoring extracellular changes in pH induced by the test compounds. (*See, e.g.*, Dunlop *et al.*, Journal of Pharmacological and Toxicological Methods 40(1):47-55 (1998).) In one embodiment, CHO cells transfected with a nGPCR-x expression vector are seeded into 12 mm capsule cups (Molecular Devices Corp.) at 4 x $10^5$ cells/cup in MEM supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 10 U/ml penicillin, and 10 μg/ml streptomycin. The cells are incubated in this medium at 37°C in 5% $CO_2$ for 24 hours.

Extracellular acidification rates are measured using a Cytosensor microphysiometer (Molecular Devices Corp.). The capsule cups are loaded into the sensor chambers of the



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microphysiometer and the chambers are perfused with running buffer (bicarbonate-free MEM supplemented with 4 mM L-glutamine, 10 units/ml penicillin, 10 μg/ml streptomycin, 26 mM NaCl) at a flow rate of 100 μl/minute. Candidate agonists or other agents are diluted into the running buffer and perfused through a second fluid path. During each 60-second pump cycle, the pump is run for 38 seconds and is off for the remaining 22 seconds. The pH of the running buffer in the sensor chamber is recorded during the cycle from 43-58 seconds, and the pump is re-started at 60 seconds to start the next cycle. The rate of acidification of the running buffer during the recording time is calculated by the Cytosoft program. Changes in the rate of acidification are calculated by subtracting the baseline value (the average of 4 rate measurements immediately before addition of a modulator candidate) from the highest rate measurement obtained after addition of a modulator candidate. The selected instrument detects 61mV/pH unit. Modulators that act as agonists of the receptor result in an increase in the rate of extracellular acidification compared to the rate in the absence of agonist. This response is blocked by modulators which act as antagonists of the receptor.

**Example 12 - Using nGPCR-x proteins to isolate neurotransmitters**

Isolated nGPCR-x proteins of the present invention can be used to isolate novel or known neurotransmitters (Saito *et al.*, Nature 400: 265-269, 1999). The cDNAs that encode the isolated nGPCR-x can be cloned into mammalian expression vectors and used to stably or transiently transfect mammalian cells including CHO, Cos or HEK293 cells. Receptor expression can be determined by Northern blot analysis of transfected cells and identification of an appropriately sized mRNA band (predicted size from the cDNA). Brain regions shown by mRNA analysis to express each of the nGPCR-x proteins could be processed for peptide extraction using any of several protocols ((Reinsheidk R.K. *et al.*, Science 270: 243-247, 1996; Sakurai, T., *et al.*, Cell 92; 573-585, 1998; Hinuma, S., *et al.*, Nature 393: 272-276, 1998). Chromotographic fractions of brain extracts could be tested for ability to activate nGPCR-x proteins by measuring second messenger production such as changes in cAMP production in the presence or absence of forskolin, changes in inositol 3-phosphate levels, changes in intracellular calcium levels or by indirect measures of receptor activation including receptor stimulated mitogenesis, receptor mediated changes in extracellular acidification or receptor mediated changes in reporter gene activation in response to cAMP or calcium (these methods should all be referenced in other sections of the patent). Receptor activation could also be monitored by co-transfecting cells with a chimeric $GI_{q/i3}$ to force receptor coupling to a calcium stimulating



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pathway (Conklin *et al.*, Nature 363; 274-276, 1993). Neurotransmitter mediated activation of receptors could also be monitored by measuring changes in [$^{35}$ S]-GTPKS binding in membrane fractions prepared from transfected mammalian cells. This assay could also be performed using baculoviruses containing nGPCR-x proteins infected into SF9 insect cells.

The neurotransmitter which activates nGPCR-x proteins can be purified to homogeneity through successive rounds of purification using nGPCR-x proteins activation as a measurement of neurotransmitter activity. The composition of the neurotransmitter can be determined by mass spectrometry and Edman degradation if peptidergic. Neurotransmitters isolated in this manner will be bioactive materials which will alter neurotransmission in the central nervous system and will produce behavioral and biochemical changes.

**Example 13 - Using nGPCR-x proteins to isolate and purify G proteins**

cDNAs encoding nGPCR-x proteins are epitope–tagged at the amino terminuus end of the cDNA with the cleavable influenza-hemagglutinin signal sequence followed by the FLAG epitope (IBI, New Haven, CT). Additionally, these sequences are tagged at the carboxyl terminus with DNA encoding six histidine residues. (Amino and Carboxyl Terminal Modifications to Facilitate the Production and Purification of a G Protein-Coupled Receptor, B.K. Kobilka , *Analytical Biochemistry*, Vol. 231, No. 1, Oct 1995, pp. 269-271). The resulting sequences are cloned into a baculovirus expression vector such as pVL1392 (Invitrogen). The baculovirus expression vectors are used to infect SF-9 insect cells as described (Guan, X. M., Kobilka, T. S., and Kobilka, B. K. (1992) *J. Biol. Chem.* **267,** 21995-21998). Infected SF-9 cells could be grown in 1000-ml cultures in SF900 II medium (Life Technologies, Inc.) containing 5% fetal calf serum (Gemini, Calabasas, CA) and 0.1 mg/ml gentamicin (Life Technologies, Inc.) for 48 hours at which time the cells could be harvested. Cell membrane preparations could be separated from soluble proteins following cell lysis. nGPCR-x protein purification is carried out as described for purification of the 92 receptor (Kobilka, Anal. Biochem., 231 (1): 269-271, 1995) including solubilization of the membranes in 0.8-1.0 % *n*-dodecyl -D-maltoside (DM) (CalBiochem, La Jolla, CA) in buffer containing protease inhibitors followed by Ni-column chromatography using chelating Sepharose™ (Pharmacia, Uppsala, Sweden). The eluate from the Ni-column is further purified on an M1 anti-FLAG antibody column (IBI). Receptor containing fractions are monitored by using receptor specific antibodies following western blot analysis or by SDS-PAGE analysis to look for an appropriate sized protein band (appropriate size would be the predicted molecular weight of the protein).

This method of purifying G protein is particularly useful to isolate G proteins that bind to the nGPCR-x proteins in the absence of an activating ligand.



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Some of the preferred embodiments of the invention described above are outlined below and include, but are not limited to, the following embodiments. As those skilled in the art will appreciate, numerous changes and modifications may be made to the preferred embodiments of the invention without departing from the spirit of the invention. It is intended that all such variations fall within the scope of the invention.

The entire disclosure of each publication cited herein is hereby incorporated by reference.



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**What is claimed is:**

1. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence homologous to sequences selected from the group consisting of: SEQ ID NO:111 to SEQ ID NO:220; said nucleic acid molecule encoding at least a portion of nGPCR-x.

2. The isolated nucleic acid molecule of claim 1 comprising a sequence that encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220.

3. The isolated nucleic acid molecule of claim 1 comprising a sequence homologous to a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110.

4. The isolated nucleic acid molecule of claim 1 comprising a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:110.

5. The isolated nucleic acid molecule of claim 1 wherein said nucleic acid molecule is DNA.

6. The isolated nucleic acid molecule of claim 1 wherein said nucleic acid molecule is RNA.

7. An expression vector comprising a nucleic acid molecule of any one of claims 1 to 4.

8. The expression vector of claim 7 wherein said nucleic acid molecule comprises a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:110.

9. The expression vector of claim 7 wherein said vector is a plasmid.

10. The expression vector of claim 7 wherein said vector is a viral particle.

11. The expression vector of claim 10 wherein said vector is selected from the group consisting of adenoviruses, baculoviruses, parvoviruses, herpesviruses, poxviruses, adeno-associated viruses, Semliki Forest viruses, vaccinia viruses, and retroviruses.



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12. The expression vector of claim 7 wherein said nucleic acid molecule is operably connected to a promoter selected from the group consisting of simian virus 40, mouse mammary tumor virus, long terminal repeat of human immunodeficiency virus, maloney virus, cytomegalovirus immediate early promoter, Epstein Barr virus, rous sarcoma virus, human actin, human myosin, human hemoglobin, human muscle creatine, and human metalothionein.

13. A host cell transformed with an expression vector of claim 7.

14. The transformed host cell of claim 13 wherein said cell is a bacterial cell.

15. The transformed host cell of claim 14 wherein said bacterial cell is E. coli.

16. The transformed host cell of claim 13 wherein said cell is yeast.

17. The transformed host cell of claim 16 wherein said yeast is S. cerevisiae.

18. The transformed host cell of claim 13 wherein said cell is an insect cell.

19. The transformed host cell of claim 18 wherein said insect cell is S. frugiperda.

20. The transformed host cell of claim 13 wherein said cell is a mammalian cell.

21. The transformed host cell of claim 20 wherein mammalian cell is selected from the group consisting of chinese hamster ovary cells, HeLa cells, African green monkey kidney cells, human HEK-293 cells, and murine 3T3 fibroblasts.

22. An isolated nucleic acid molecule comprising a nucleotide sequence complementary to at least a portion of a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:110, said portion comprising at least 10 nucleotides.

23. The nucleic acid molecule of claim 22 wherein said molecule is an antisense oligonucleotide directed to a region of a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:110.



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24. The nucleic acid molecule of claim 23 wherein said oligonucleotide is directed to a regulatory region of a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:110.

25. A composition comprising a nucleic acid molecule of any one of claims 1 to 4 or 22 and an acceptable carrier or diluent.

26. A composition comprising a recombinant expression vector of claim 7 and an acceptable carrier or diluent.

27. A method of producing a polypeptide that comprises a sequence selected from the group of sequences consisting SEQ ID NO:111 to SEQ ID NO:220, and homologs thereof, said method comprising the steps of:

a) introducing a recombinant expression vector of claim 8 into a compatible host cell;

b) growing said host cell under conditions for expression of said polypeptide; and

c) recovering said polypeptide.

28. The method of claim 27 wherein said host cell is lysed and said polypeptide is recovered from the lysate of said host cell.

29. The method of claim 27 wherein said polypeptide is recovered by purifying the culture medium without lysing said host cell.

30. An isolated polypeptide encoded by a nucleic acid molecule of claim 1.

31. The polypeptide of claim 30 wherein said polypeptide comprises a sequence selected from the group of sequences consisting of SEQ ID NO:111 to SEQ ID NO:220.

32. The polypeptide of claim 30 wherein said polypeptide comprises an amino acid sequence homologous to a sequence selected from the group of sequences consisting of SEQ ID NO:111 to SEQ ID NO:220.



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33. The polypeptide of claim 30 wherein said sequence homologous to a sequence selected from the group of sequences consisting of SEQ ID NO:111 to SEQ ID NO:220 comprises at least one conservative amino acid substitution compared to the sequences in the group of sequences consisting of SEQ ID NO:111 to SEQ ID NO:220.

34. The polypeptide of claim 30 wherein said polypeptide comprises an allelic variant of a polypeptide with a sequence selected from the group of sequences consisting of SEQ ID NO:111 to SEQ ID NO:220.

35. A composition comprising a polypeptide of claim 34 and an acceptable carrier or diluent.

36. An isolated antibody which binds to an epitope on a polypeptide of claim 30.

37. The antibody of claim 36 wherein said antibody is a monoclonal antibody.

38. A composition comprising an antibody of claim 36 and an acceptable carrier or diluent.

39. A method of inducing an immune response in a mammal against a polypeptide of claim 30 comprising administering to said mammal an amount of said polypeptide sufficient to induce said immune response.

40. A method for identifying a compound which binds nGPCR-x comprising the steps of:

a) contacting nGPCR-x with a compound; and

b) determining whether said compound binds nGPCR-x.

41. The method of claim 40 wherein the nGPCR-x comprises an amino acid sequence selected from the group consisting of SEQ ID NO:SEQ ID NO:111 to SEQ ID NO:220.

42. The method of claim 40 wherein binding of said compound to nGPCR-x is determined by a protein binding assay.

43. The method of claim 40 wherein said protein binding assay is selected from the group consisting of a gel-shift assay, Western blot, radiolabeled competition assay, phage-based expression cloning, co-fractionation by chromatography, co-precipitation, cross linking, interaction trap/two-hybrid analysis, southwestern analysis, and ELISA.



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44. A compound identified by the method of claim 40.

45. A method for identifying a compound which binds a nucleic acid molecule encoding nGPCR-x comprising the steps of:

a) contacting said nucleic acid molecule encoding nGPCR-x with a compound; and

b) determining whether said compound binds said nucleic acid molecule.

46. The method of claim 45 wherein binding is determined by a gel-shift assay.

47. A compound identified by the method of claim 45.

48. A method for identifying a compound which modulates the activity of nGPCR-x comprising the steps of:

a) contacting nGPCR-x with a compound; and

b) determining whether nGPCR-x activity has been modulated.

49. The method of claim 48 wherein the nGPCR-x comprises an amino acid sequence selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220.

50. The method of claim 48 wherein said activity is neuropeptide binding.

51. The method of claim 48 wherein said activity is neuropeptide signaling.

52. A compound identified by the method of claim 48.

53. A method of identifying an animal homolog of nGPCR-x comprising the steps:

a) comparing the nucleic acid sequences of the animal with a sequence selected from the group of sequence consisting of SEQ ID NO:1 to SEQ ID NO:110, and portions thereof, said portions being at least 10 nucleotides; and

b) identifying nucleic acid sequences of the animal that are homologous to said sequence selected from the group sequence consisting of SEQ ID NO:1 to SEQ ID NO:110, and portions thereof, said portions comprising at least 10 nucleotides.



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54. The method of claim 53 wherein comparing the nucleic acid sequences of the animal with a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:110, and portions thereof, said portions being at least 10 nucleotides, is performed by DNA hybridization.

55. The method of claim 53 wherein comparing the nucleic acid sequences of the animal with a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:110, and portions thereof, said portions being at least 10 nucleotides, is performed by computer homology search.

56. A method of screening a human subject to diagnose a disorder affecting the brain or genetic predisposition therefor, comprising the steps of:

(a) assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering an amino acid sequence, expression, or biological activity of at least one nGPCR-x that is expressed in the brain, wherein the nGPCR-x comprises an amino acid sequence selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220, and allelic variants thereof, and wherein the nucleic acid corresponds to a gene encoding the nGPCR-x; and

(b) diagnosing the disorder or predisposition from the presence or absence of said mutation, wherein the presence of a mutation altering the amino acid sequence, expression, or biological activity of the nGPCR-x in the nucleic acid correlates with an increased risk of developing the disorder.

57. A method according to claim 56, wherein the disease is a mental disorder.

58. A method according to claim 56, wherein the assaying step comprises at least one procedure selected from the group consisting of:

a) comparing nucleotide sequences from the human subject and reference sequences and determining a difference of at least a nucleotide of at least one codon between the nucleotide sequences from the human subject that encodes a nGPCR-x reference sequence;

(b) performing a hybridization assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences;



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(c) performing a polynucleotide migration assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences; and

(d) performing a restriction endonuclease digestion to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences.

59. A method according to claim 58 wherein the assaying step comprises: performing a polymerase chain reaction assay to amplify nucleic acid comprising nGPCR-x coding sequence, and determining nucleotide sequence of the amplified nucleic acid.

60. A method of screening for an nGPCR-x hereditary mental disorder genotype in a human patient, comprising the steps of:

(a) providing a biological sample comprising nucleic acid from said patient, said nucleic acid including sequences corresponding to alleles of nGPCR-x; and

(b) detecting the presence of one or more mutations in the nGPCR-x allele;

wherein the presence of a mutation in a nGPCR-x allele is indicative of a hereditary mental disorder genotype.

61. The method according to claim 60 wherein said biological sample is a cell sample.

62. The method according to claim 60 wherein said detecting the presence of a mutation comprises sequencing at least a portion of said nucleic acid, said portion comprising at least one codon of said nGPCR-x allele, said portion comprising at least 10 nucleotides.

63. The method according to claim 60 wherein said nucleic acid is DNA.

64. The method according to claim 60 wherein said nucleic acid is RNA.

65. A kit for screening a human subject to diagnose a mental disorder or a genetic predisposition therefor, comprising, in association:

(a) an oligonucleotide useful as a probe for identifying polymorphisms in a human nGPCR-x gene, the oligonucleotide comprising 6-50 nucleotides in a sequence that is identical or complementary to a sequence of a wild type human nGPCR-x gene sequence or



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nGPCR-x coding sequence, except for one sequence difference selected from the group consisting of a nucleotide addition, a nucleotide deletion, or nucleotide substitution; and

(b) a media packaged with the oligonucleotide, said media containing information for identifying polymorphisms that correlate with mental disorder or a genetic predisposition therefor, the polymorphisms being identifiable using the oligonucleotide as a probe.

66. A method of identifying a nGPCR-x allelic variant that correlates with a mental disorder, comprising the steps of:

(a) providing a biological sample comprising nucleic acid from a human patient diagnosed with a mental disorder, or from the patient's genetic progenitors or progeny;

(b) detecting in the nucleic acid the presence of one or more mutations in an nGPCR-x that is expressed in the brain, wherein the nGPCR-x comprises an amino acid sequence selected from the group consisting of SEQ ID NO:111 to SEQ ID NO:220, and allelic variants thereof, and wherein the nucleic acid includes sequence corresponding to the gene or genes encoding nGPCR-x;

wherein the one or more mutations detected indicates an allelic variant that correlates with a mental disorder.

67. A purified and isolated polynucleotide comprising a nucleotide sequence encoding a nGPCR-x allelic variant identified according to claim 66.

68. A host cell transformed or transfected with a polynucleotide according to claim 67 or with a vector comprising the polynucleotide.

69. A purified polynucleotide comprising a nucleotide sequence encoding nGPCR-x of a human with a mental disorder;

wherein said polynucleotide hybridizes to the complement of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110 under the following hybridization conditions:

(a) hybridization for 16 hours at 42°C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% dextran sulfate and

(b) washing 2 times for 30 minutes at 60°C in a wash solution comprising 0.1x SSC and 1% SDS; and



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wherein the polynucleotide that encodes nGPCR-x amino acid sequence of the human differs from the sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110 by at least one residue.

70. A vector comprising a polynucleotide according to claim 69.

71. A host cell that has been transformed or transfected with a polynucleotide according to claim 69 and that expresses the nGPCR-x protein encoded by the polynucleotide.

72. A host cell according to claim 71 that has been co-transfected with a polynucleotide encoding the nGPCR-x amino acid sequence set forth in a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:110 and that expresses the nGPCR-x protein having the amino acid sequence set forth in SEQ ID NO:111 to SEQ ID NO:220.

73. A method for identifying a modulator of biological activity of nGPCR-x comprising the steps of:

a) contacting a cell according to claim 72 in the presence and in the absence of a putative modulator compound;

b) measuring nGPCR-x biological activity in the cell;

wherein decreased or increased nGPCR-x biological activity in the presence versus absence of the putative modulator is indicative of a modulator of biological activity.

74. A method to identify compounds useful for the treatment of a mental disorder, said method comprising the steps of:

(a) contacting a composition comprising nGPCR-x with a compound suspected of binding nGPCR-x;

(b) detecting binding between nGPCR-x and the compound suspected of binding nGPCR-x;

wherein compounds identified as binding nGPCR-x are candidate compounds useful for the treatment of a mental disorder.

75. A method for identifying a compound useful as a modulator of binding between nGPCR-x and a binding partner of nGPCR-x comprising the steps of:

(a) contacting the binding partner and a composition comprising nGPCR-x in the presence and in the absence of a putative modulator compound;



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(b) detecting binding between the binding partner and nGPCR-x;

wherein decreased or increased binding between the binding partner and nGPCR-x in the presence of the putative modulator, as compared to binding in the absence of the putative modulator is indicative a modulator compound useful for the treatment of a mental disorder.

76. A method according to claim 74 or 75 wherein the composition comprises a cell expressing nGPCR-x on its surface.

77. A method according to claim 76 wherein the composition comprises a cell transformed or transfected with a polynucleotide that encodes nGPCR-x.

78. A method of purifying a G protein from a sample containing said G protein comprising the steps of:

a) contacting said sample with a polypeptide of claim 1 for a time sufficient to allow said G protein to form a complex with said polypeptide;

b) isolating said complex from remaining components of said sample;

c) maintaining said complex under conditions which result in dissociation of said G protein from said polypeptide; and

d) isolating said G protein from said polypeptide.

79. The method of claim 78 wherein said sample comprises an amino acid sequence selected from the group of sequences consisting of SEQ ID NO:111 to SEQ ID NO:220.

80. The method of claim 78 wherein said polypeptide comprises an amino acid sequence homologous to a sequence selected from the group of sequences consisting of SEQ ID NO:111 to SEQ ID NO:220.

81. The method of claim 78 wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO:111 to SEQ ID NO:220.



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Vogeli, Gabriel
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Parodi, Luis
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tatatttata taaatattta tataaatata taaaaatata tttatataaa tatatttata 660

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gtgactgcta atgagtgctg gtgtcttttt ggggtgatgg ctgcacaact ctctacatat 360

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<212> DNA
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aaatgaggaa actgcattct gtattatata aagatttaat tttatcatga gctttggaac 540

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<212> DNA
<213> Homo sapiens

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<211> 456
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aatactatcg tagtcacagt atgccacaaa aaaacaaata actcacaacc aacatggtgt 180

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<211> 399
<212> DNA
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<211> 619
<212> DNA
<213> Homo sapiens

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<210> 43
<211> 473
<212> DNA
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aacaaaatat gcccgtgatg agtaaagaga tataaaatct tatcagacac agaaagtaaa 240

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<210> 44



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<212> DNA
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gtgatgatta cagaaggaaa atggtcaagg agtgattcct ttggttatcc tccaaatggc 480

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attatgataa aggattatta ttatgttaaa atgtttatac actgaataca taaatttgta 720

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<211> 578
<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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accaggtggg acagagggca cagagaaagc tctcaatact catggccacc aggagacaga 240

gacccactgt gtcggagaaa taggagacag gatccagaaa cacagccacc tgcaatgccg 300

cctggtgata cagcatgagg attttctcca gcaggatcac agttacacag gagaggttga 360

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<211> 638
<212> DNA
<213> Homo sapiens

<400> 50
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ccaatcatca ttcattggac aaacagattc tcaatatt 638

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tacactgctt tggaagtgat caccaggata aatgaacaaa acaaggtaga aaaggatata 180

tgtaataata tataatcctt taaggaatgg ggaggggcaa atgtaattat atttgcttat 240

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<211> 570
<212> DNA
<213> Homo sapiens

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gccaggattt taacgcaagt tgtccagact ccaagggcca gattctcctc tgacattaac 420

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<211> 600
<212> DNA
<213> Homo sapiens

<400> 53
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<212> DNA
<213> Homo sapiens

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catattgtat atactttgca ttattgccta attccttgtg cctgagttta ttgtataaat 540

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<210> 55
<211> 619
<212> DNA
<213> Homo sapiens

<400> 55
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cagctgtttc ccatttgagg taaaggggta tacaaacaat actgctatga acactcttca 180

gcatgactgc aaatattcat gaccaagaat ttctcccaag cagtgttttt caaactgcag 240

actgcaatct agtaatgggt cattaaatcg atttagttac aataagtggc attttttttaa 300

acggattata atacaataga aaatatcaag gtaataggca cacattctta gcaatgaaac 360

tacagttaaa ggaataaact tataaaacag acatgcttca taaattattt tctaaatttt 420

tatcatgttt aagattttta ttgtatttaa atattagtaa attcacattt gatataaaca 480

ttttcatata tttaccttaa ttatatgtag taaaaataac ttatacgaaa cttacttcat 540

gtgtgtataa tgggtcatga agtaaaatgt acttcagcgt gggggatcat actaacaaaa 600

gtttgaagaa cacttctct 619

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<211> 659
<212> DNA
<213> Homo sapiens

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ccaagttaca ctgctggtaa gaagccctac ttcatcaaca acaactacac ttgaaacaat 240

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<213> Homo sapiens

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225                 230                 235                 240

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Cys Ala Ala Cys Ala Cys Gly Thr Gly Cys Ala Thr Gly Cys Thr Gly
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Cys Thr Thr Thr Ala Ala Cys Thr Thr Gly Ala Ala Thr Thr Gly Ala
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Cys Ala Ala Gly Cys Ala Ala Gly Cys Cys Cys Thr Thr Ala Ala Cys
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Thr Ala Thr Thr Thr Thr Ala Cys Thr Thr Ala Gly Ala Cys Thr Gly
420 425 430

Cys Thr Thr Thr Ala Cys Thr Thr Ala Cys Ala Thr Cys Thr Thr Thr
435 440 445

Cys Cys Cys Cys Ala Thr Thr Cys Thr Ala Gly Cys Thr Cys Ala Gly
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485 490 495

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tggagacgtt tcaacatgaa ttttggagag acagaaacac ccaaaccata acagaaatga 180

aaagggaagg gagtgatagg ttgcagaaaa gggagaggtt aaggataaat gagatgtgag 240

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gaacaggcac caaactgcct aatcatggga acatgttatc aacattttcc caggcagcag 300

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<211> 475
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<212> DNA
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<212> DNA
<213> Homo sapiens

<400> 102
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<400> 105

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Cys Ala Thr Thr Cys Ala Cys Cys Thr Cys Thr Thr Thr Gly Thr Ala
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85 90 95

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115 120 125

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130 135 140

Gly Thr Gly Ala Ala Gly Thr Thr Ala Gly Cys Thr Thr Thr Gly Gly
145 150 155 160

Cys Cys Ala Gly Gly Thr Gly Ala Thr Cys Thr Cys Thr Gly Cys Ala
165 170 175

Thr Ala Thr Cys Ala Gly Ala Cys Thr Ala Thr Thr Ala Ala Ala Gly
180 185 190

Gly Cys Ala Gly Cys Gly Cys Cys Thr Thr Thr Ala Cys Ala Gly Ala
195 200 205

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210 215 220

Gly Ala Cys Thr Cys Ala Thr Gly Cys Thr Thr Thr Gly Cys Thr Thr
225 230 235 240

Thr Gly Cys Ala Cys Thr Cys Cys Cys Thr Ala Ala Ala Gly Ala Gly
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325 330 335

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340 345 350

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435 440 445

Ala Gly Ala Ala Cys Ala Ala Cys Thr Ala Gly Thr Thr Thr Thr Gly
450 455 460

Gly Gly Ala Ala Thr Thr Thr Gly Thr Cys Cys Thr Ala Cys Ala Thr
465 470 475 480

Ala Gly Thr Cys Ala Thr Ala Thr Gly Ala Cys Thr Cys Ala Thr Cys
485 490 495

Thr Gly Cys Ala Thr Ala Gly Ala Thr Cys Cys Thr Ala Ala Thr Ala
500 505 510

Thr Gly Ala Thr Cys Ala Thr Ala Gly Cys Thr Thr
515 520

<210> 106
<211> 346
<212> DNA
<213> Homo sapiens

<400> 106
tcttcccttg ttttatctta tatcaaactc tataaggaat aggatcacac agctcctaat 60

aaggaggagc ataaggtaaa atcatgcaca gcattttagt tagaaaatat taatctttat 120

gttttcattt cttagtcttt taaataataa aaatgcatcg aaatgtttaa aactttaaat 180



BNSDOCID <WO 0162924A2 I >

attgtaaaag ttatagtaag acacgttgcc aactagattc atgcatctaa tttcctgaat 240

tatagttaat agtttcatat tataaactct tgataaaagt aataaataca tggcagatac 300

acacatgcac atttgtatta tataatagta gtccagtgaa cgcttc 346

<210> 107
<211> 578
<212> DNA
<213> Homo sapiens

<400> 107
ctcacatatt accttcaaag aaacctgtcc taataaaagc cattcctact ctacttggcc 60

tccaggattt aaccacttcc tacattcaac catcctggga cctagcttta ctagacttca 120

attttgacct tatttatctt gccttttgtc ataattgctt cttgctttcg tgctccatta 180

aacactaagg tttttgagag caggaactca aaacacttta aattcctctc tcttcatatg 240

cagttgcttt tgcacagtca atacacagta aatgctgatt gaattgaaag gatctcactc 300

ttagaatgca attctctcag agtctccaac tagtctagta gcttaaagac caatcctact 360

taaaaattaa cttgaattgt aagtacaaca aaatcactcc aagttattaa cctaaccatt 420

gaagtgttta ttttcctact tggaaaacca ggtcaaccac agggaccaac ctaccctgga 480

taggtgactc taaaagtaat gaggtaattt ccttcaaaaa tgacaaagct ttcaggattc 540

tctggaatgc atacccatta atgtgtcacc attaatca 578

<210> 108
<211> 692
<212> DNA
<213> Homo sapiens

<400> 108
gggcaagggt gatggaggtt tgaggagaca ggagaaagtg ggaaaagtag ttcgaatcaa 60

tgaattcatt tttggaatac agtaggatta ccaggtttgt gctcataatt taaagtgaga 120

ccagtcaaca gtgttgcaat ttccttatag ccatttcagc tactcaagcc catgtgtgga 180

ataaacagac agtctgattc aactagggac ggagtttgcc cgagggcata accactaaac 240

agaagaaaaa aggagaaagg gaggggtgac tgcactcaaa aaatacaata agtaggtatt 300

tacctggctt acgttctaaa agctgctgta aatgaaacac tgcttgttca tagtcttgtt 360

ttctgaacat gagatcagcc atcatctata aagataaaag ttggttctaa aaatattgcc 420

atgtatttta cacaacatgt tcttccaatc aagatttagc actagaaaaa tatagatgat 480

aaacatgagg agggggcagc attttataaa aaggaggcat ttaagattca agcccacctt 540

gtgcagaata acttgcagat cagtgtaaca gaagataatc aaggatgtga aacagattgc 600



BNSDOCID <WO __0162924A2 I >

tctgcttgca aaattgtatt tttagcaaaa aatatgtttc tagcaattgt tttaaaaaca 660

gaaatttgaa ggaattgcac actctatgtg ct 692

<210> 109
<211> 674
<212> DNA
<213> Homo sapiens

<400> 109
actttgtcct atgcatcttt tcccttggtt aatctgtgtc tgtatcctct ccctgtaata 60

aactgtaatc gcaagtgagc tgctttcagt gagtttttg agtgttccta gtaaattatc 120

aaacctgaag gggatttggg gaactccttg aatttgcaat tggtgttagg agtgaagaca 180

atcttgtgtg taccgtgttc tctctaactt tatggggttt aggcatggtg ggtggtagag 240

aatgaagtag gtgtgtaaaa ttaactgtga tctgattctt acctaaaaaa aaactttccc 300

catagcaggg ctgatataaa gaagccacaa cttaggtttt tcctactttg cacacaaaat 360

tccaacagtg gaacttctga atgatttact taggaaatta catatggaga aatgttttga 420

aactacaaat tctcaccaaa gatttcctaa aatactccaa taaggtgata gactgtaatc 480

agaactcaca tttaccaaaa aggagatggt attctatttt gaaagtaatt atattactgg 540

gaaaacaatg tttaccagtt ttaattataa tactggaaac aacagttttt ataaatgttt 600

ctgaatgaat ttacaattta aatgaataaa tccttatgcc taaaatgaac actgggcaca 660

tttttaagca ctac 674

<210> 110
<211> 579
<212> DNA
<213> Homo sapiens

<400> 110
tatacttaag attatttctt tggacactgt tctgttatag taatgtgtct gatcctacag 60

aagtaccata gtattttaat cattataatt tccaatataa gttatacgtg atagatcaag 120

ttctttataa ttttttcttc ttcagagttt tatctggaat ttattctggt gtttgatatg 180

acataaatat ctaatttgtc tcccaaacag agtcaagatg attcctgtaa tgttactaat 240

ttgtgttctg agaaggaaga aaagtggcag cactatggca ctgggaattc tgcataaacc 300

catgaaagca gtcacctttg tgaacgtgtt tttggtggaa acaagtgttg agaaccattg 360

ttgtataata gtgctgtcca gtagaactta ctctggtgat gggaatactc tatagctgta 420

ctttccaata tggtattcac tgaccacatg tggctatcaa gtacttgaaa tgtggctagg 480



BNSDOCID <WO _ 0162924A2 I_>

tgactgagga accgaaattt ttagtcttat ttaattgtaa tcagtttaaa tttatacaac 540

tgcatatttt attgaataga gcactttcta gagcatagc 579

<210> 111
<211> 199
<212> PRT
<213> Homo sapiens

<400> 111

Gln Ile Pro Ser Phe Ser Pro Leu Thr Asn Glu Leu Leu Leu Phe Pro
1 5 10 15

Trp Thr Gly Tyr Glu Ile Arg Gln Phe Asn Pro Leu Ile Tyr Asp Asn
20 25 30

Gly Arg Asp Val Ala Glu Asn Pro Glu Leu Ser Val Leu Leu Ile Lys
35 40 45

Thr Thr Leu Val Met Val Thr Lys Gly Lys Tyr Ile Pro Leu Met Ser
50 55 60

Arg Phe Thr Leu Ser Leu Thr Met Thr Gln Leu Cys Gly Ala Glu Ser
65 70 75 80

Asn Thr Ala Ser Leu Ile Leu Leu Gln His Lys Ile Tyr Ser Glu Ser
85 90 95

Asp Lys Trp Ile Asn Leu His Met Asp Glu His Asp Leu Leu Leu Ser
100 105 110

Lys Val Pro Lys Asp Thr Glu Lys Asn Leu Val Met Leu Leu Asp Asp
115 120 125

Val Phe Asp Asn Thr Ile Gln Tyr Leu Ser Met Tyr Pro Tyr Asp Ile
130 135 140

Glu Lys Gly Phe Ser Lys Tyr Phe Asn Leu Asn Arg Phe Thr Lys Arg
145 150 155 160

Asn His Leu Pro Thr Thr Val Pro Cys Leu Trp Ser Ile Arg Val Ile
165 170 175

Ile Leu Phe Ser Leu Tyr Tyr Lys Arg Glu Cys Thr Leu Phe Lys Ile
180 185 190

Asn Asn Ile Asp Tyr Ile Ser
195

<210> 112
<211> 231
<212> PRT
<213> Homo sapiens

<400> 112

Glu Leu Lys Thr Glu Asn Val Cys Lys Tyr Val Lys Tyr Val Tyr Lys



BNSDOCID <WO _0162924A2_I_>

1 5 10 15

Asn Met Tyr Phe Ser Tyr Phe Lys Ser Phe Ile Leu Tyr Ile Thr His
20 25 30

Thr His Thr His Thr His Thr Met Arg Ser Leu Leu Thr Thr Gln Tyr
35 40 45

Lys Ile Ile Phe Leu Arg Asn Ile Val Phe Lys Tyr Cys Phe Ile Pro
50 55 60

Tyr Lys Ser Asn Leu Trp Leu Phe Tyr Gly Phe His Gln Ala Met Ser
65 70 75 80

Leu Thr Asn Phe Ala Asn Lys Gly Thr Gln Gly Met Lys Tyr Leu Leu
85 90 95

Thr Asn Lys Lys Pro Ser Asn Ser Met Tyr Val Ile Gly Lys Ile Lys
100 105 110

Ser Ser Val Asn Ser Ile His Glu Leu Thr Ser Ile Ser Ala Leu Leu
115 120 125

Ser Leu Lys Ile Ser Asn Ser Leu Lys Ile Ile Arg Thr His Leu Asn
130 135 140

Val Ser Ser Thr Trp Ile Gly Cys Leu Phe Ser Ile Arg Thr Glu Arg
145 150 155 160

Tyr Leu Leu Asp Ile Phe Tyr Thr His Lys Arg Phe Lys Lys Leu Ile
165 170 175

Asn Arg Ser Arg Leu His Val Asn Ser Leu Ser Asp Ser Ser Glu Leu
180 185 190

Ser Ile Ala Lys Arg Leu Ser Asn Arg Arg Asp His Ala Leu Ser Phe
195 200 205

Leu Arg Gly Pro Cys Cys Ile Thr Val Leu Gln Phe Leu Gln Arg Arg
210 215 220

Thr Leu Lys Lys Thr Thr Leu
225 230

<210> 113
<211> 211
<212> PRT
<213> Homo sapiens

<400> 113

Trp Phe Val Ile Ile Val Gly Cys Phe Ile Ile Thr Phe Tyr Asn Leu
1 5 10 15

Tyr Ser Phe Ser Ile Thr Tyr Val Ala Ile Ser Met Ser Leu Tyr Leu
20 25 30

His Gln Tyr Leu Leu Ile Tyr Ile Glu Ile Lys Phe Ser Leu Gln Arg
35 40 45



BNSDOCID <WO__0162924A2_I_>

Ser Arg Arg His Pro Leu Ile Ser His Ile Asp Tyr Trp Leu Leu Thr
50 55 60

Ser Asn Leu Ser Pro Cys Tyr Val Ala Pro Arg Glu Met Tyr Thr Leu
65 70 75 80

Leu Ser Gln Val Ile Leu Ile Cys Thr Glu Ser Leu Thr Ser Leu Lys
85 90 95

Leu Leu Val Val Ser His Tyr Leu Thr Lys Phe Lys Pro Tyr Asp Val
100 105 110

Gln Thr Leu Ser Trp Leu Phe Phe Ile Phe Pro Ile Leu Leu Tyr Ser
115 120 125

Phe Tyr Leu Ser Gln Thr Ala Ala Ile Ser Asp Phe Leu Gln Phe Cys
130 135 140

Lys Ser Thr Lys Trp Leu Cys Arg Ser Asn Tyr Val Phe Thr Tyr Leu
145 150 155 160

His Leu His Arg Met Leu Phe Leu Ile Leu Cys Phe Ser Gly Glu Asp
165 170 175

Leu Ile Leu Phe Glu Gly Asn Ala Leu His Lys Asn Ser Ser Phe Ser
180 185 190

Pro Gln Asn Glu Val Leu Thr Phe Ile Phe Trp Val Leu Thr Leu Asn
195 200 205

Val His Thr
210

<210> 114
<211> 159
<212> PRT
<213> Homo sapiens

<400> 114

Ser Arg Tyr Thr Thr Leu Leu Met Lys Ser Ser Tyr Arg Ser Glu Lys
1 5 10 15

His Phe Phe Pro Thr Asn Leu Ile Leu Glu Leu Asn Thr Leu His Gln
20 25 30

Val Asp His Lys Leu His Leu Ile Asn Ala Gln Cys Leu Thr Met Ser
35 40 45

Trp Ile Val Ser Gln Gly Gln Val Lys Ala Cys Thr Arg Gly Glu Val
50 55 60

Arg Glu His Thr Ala Phe Tyr Lys Ser Thr Ile Val Pro Ile Leu Gln
65 70 75 80

Trp Leu Leu His Ile Leu Leu Thr Phe Leu Phe Ser Phe Phe Cys Trp
85 90 95



BNSDOCID <WO 0162924A2 I >

Phe Ala Leu Asn Pro Pro Leu Ser Lys Asp Ile Arg Met Tyr His Leu
100 105 110

His Ser Leu Cys Gln Asn Cys Lys Met Pro Phe Ile Phe Leu Asp Met
115 120 125

Ser Gln Ile Ala Lys Lys Met Lys Ile Leu His Phe Leu Phe Ile Leu
130 135 140

Ser Pro Gln Thr Ser Ser Thr Cys Phe Ala Val Leu Arg Gly Glu
145 150 155

<210> 115
<211> 205
<212> PRT
<213> Homo sapiens

<400> 115

Ile Asn Val Ala Asn Asn Lys Asn Leu Phe Cys Ser Ser Ser Gly Gly
1 5 10 15

Lys Ser Lys Glu Asn Gln Gly Val Ser Arg Met Glu Ala Leu Glu Ser
20 25 30

Arg Glu Glu Phe Phe Ile Phe Ser Leu Leu Leu Val Ala Pro Ser Asn
35 40 45

Leu Gly Ile Pro Trp Phe Val Ala Ala Ser Leu Gln Phe Leu Pro Ser
50 55 60

Ser Phe His Glu Leu Ile Ser Cys Val Cys Leu Cys Ile Ser Ser Leu
65 70 75 80

Phe Met Gly Cys Gln Leu Leu Asp Leu Arg Pro Thr Leu Thr Gln Tyr
85 90 95

Glu Leu Ile Leu Thr Leu His Leu Gln Arg Pro Tyr Leu Gln Ile Arg
100 105 110

Ser Pro Ser Glu Val Leu Gly Arg His Thr Phe Trp Gly Asp Thr Ile
115 120 125

Gln Leu Ile Thr Pro Gln Pro Pro Lys Leu Glu Arg Ala Asn Thr Glu
130 135 140

Asn His Arg Leu Gln Gly Ala Glu Ala Ser Lys Cys Asn Thr Lys His
145 150 155 160

Leu Asn Asn Asn His Ile Ala Gly Gly Trp Ser Val Asp Leu Glu Thr
165 170 175

Lys Leu Leu Arg Ala Thr Cys Gly Glu Asp Thr His Phe His Lys Phe
180 185 190

Tyr Leu Glu Pro His Gln Val Leu Met Ile Lys Cys Glu
195 200 205

<210> 116



BNSDOCID <WO 0162924A2 I >

<211> 216
<212> PRT
<213> Homo sapiens

<400> 116

Lys Thr Gly Ile Val Leu Asn Ile Phe Ile Leu Leu Leu Val Glu Trp
1 5 10 15

Met Val Ile Lys Leu Gly Gly Thr Lys Arg Lys Ser Leu Gly Ile Gln
20 25 30

Asp Leu Gln Thr Phe Phe Ser Thr Pro Glu Gln His Leu Leu Leu Leu
35 40 45

Cys Cys Tyr Phe Leu Ile Thr Ile Ser Val His Phe Cys Val Ser Gly
50 55 60

Leu Ser Glu Thr Leu Ser Ala Leu Arg Ala Gln Val Cys Gly Cys Leu
65 70 75 80

Cys Val Cys Val Cys Val Cys Ile Tyr Ile Tyr Ile Phe Met Tyr Val
85 90 95

Cys Val Tyr Ser Leu Phe Arg Pro Phe Phe Lys Leu Phe Ala Val Leu
100 105 110

His Leu Arg Ile Tyr Thr Val Phe Tyr Leu Ser Phe Leu Asn Val Tyr
115 120 125

Arg Tyr Lys Thr Glu Tyr Phe Gln Glu Trp Lys Ser Ile Phe Arg Tyr
130 135 140

Ile Ser Gln Tyr His Ala Val Glu Cys Ser Asn Leu Leu Gln Phe Thr
145 150 155 160

Ser Ile Asn Leu Val Gly Asn Cys Gly Lys Val Trp Val Ser Thr Arg
165 170 175

Lys Gln Ile Gln Ala Leu Glu Ile Leu Ile Pro Phe Leu Gly Phe Pro
180 185 190

Phe Gly Leu Leu His Cys Tyr Pro Phe Cys Lys Thr Ser Thr Pro Phe
195 200 205

Val Ser Ile Cys Ser Thr Asn Ala
210 215

<210> 117
<211> 237
<212> PRT
<213> Homo sapiens

<400> 117

Tyr Phe Leu Pro Ala Phe Ile Ser Gly Glu Leu Met Thr Asn Val Lys
1 5 10 15

Asn Glu Glu Leu Arg Leu Lys Ile Leu Glu Thr Arg Tyr Ala Pro Lys



BNSDOCID <WO__0162924A2_I_>

20 25 30

Gln Val Thr Val Met Leu Leu Ser Ile Ala Ile Ile Ser Ala Leu Leu
35 40 45

Trp Leu Pro Glu Trp Val Ala Trp Leu Trp Val Trp His Leu Lys Ala
50 55 60

Ala Gly Pro Ala Pro Pro Gln Gly Phe Ile Ala Leu Ser Gln Val Leu
65 70 75 80

Met Phe Ser Ile Ser Ser Ala Asn Pro Leu Ile Phe Leu Val Met Ser
85 90 95

Glu Glu Phe Arg Glu Gly Leu Lys Gly Val Trp Lys Trp Met Ile Thr
100 105 110

Lys Lys Pro Pro Thr Val Ser Glu Ser Gln Glu Thr Pro Ala Gly Asn
115 120 125

Ser Glu Gly Leu Pro Asp Lys Val Pro Ser Pro Glu Ser Pro Ala Ser
130 135 140

Ile Pro Glu Lys Glu Lys Pro Ser Ser Pro Ser Ser Gly Lys Gly Lys
145 150 155 160

Thr Glu Lys Ala Glu Ile Pro Ile Leu Pro Asp Val Glu Gln Phe Trp
165 170 175

His Glu Arg Asp Thr Val Pro Ser Val Gln Asp Asn Asp Pro Ile Pro
180 185 190

Trp Glu His Glu Asp Gln Glu Thr Gly Glu Gly Val Lys Ile Val Ser
195 200 205

Lys Gln Asn Lys Leu Leu Leu Tyr Leu Leu Val Leu Leu Leu Ile Asn
210 215 220

Ile Ala Asp Phe Thr Asn Tyr Asn Tyr Tyr His Glu Leu
225 230 235

<210> 118
<211> 216
<212> PRT
<213> Homo sapiens

<400> 118

Leu Leu Pro Tyr Pro Gly Val His Leu Phe Ala Glu Pro Leu Leu Leu
1 5 10 15

Gly Leu Ser Pro Cys Ser Ser Leu Trp Ser Phe Ser Asn Arg Gly Arg
20 25 30

Met Ala Ala Asp Pro Leu Pro Pro Ala Arg Arg Arg Asn Arg Arg Gly
35 40 45

Val Lys Val Pro Asp Gln Ile Gly His Pro Arg Pro Gln Gln Ala Gln
50 55 60



BNSDOCID <WO 0162924A2 I >

Gln Cys Thr Ser Val Gln Ala Ala Pro Phe Ala Gly Val Thr Met Pro
65 70 75 80

Ser Pro Thr Gly Cys Leu Cys Phe Tyr Gly Asp Phe Cys Thr Leu Ile
85 90 95

Leu Thr Arg Cys Thr Asn Gly Val Gly Met Gly Leu Trp Gln Lys Ala
100 105 110

Val Ala Ser Val Ile Phe Ala Ser Pro Arg Phe Gln Leu Ser Thr Arg
115 120 125

Pro Leu Val Ala His Phe Leu Leu Ile Thr Phe Val Pro Val Asp Pro
130 135 140

Asp Tyr Ser Leu Cys Ser Ala Ala Leu Gly Gly Leu Ser Leu Val Ala
145 150 155 160

Ser Arg Pro Leu Leu Trp Ser Lys Ser Pro Ala Lys Leu Asn Ser Ser
165 170 175

Val Val Gln Asn Arg Phe His Leu Gln Glu Lys Asn Lys Met Thr Gln
180 185 190

Ile Val Thr His Pro Asn His Thr Val Gln Arg Val Lys Val Asp Ile
195 200 205

Ala Ala Ala Ser Arg Leu Asp Ile
210 215

<210> 119
<211> 208
<212> PRT
<213> Homo sapiens

<400> 119

Glu Ser Val His Gly Arg Pro Tyr Val Pro Gly Thr Gly Tyr Val Leu
1 5 10 15

Gly Lys His Leu His Lys Ala Gln Asn Cys Leu Ser His Ser Lys His
20 25 30

Glu Phe Trp Gly Arg Gly Asn Arg Asp Asn Lys Val Ile Thr Met Glu
35 40 45

Ser Leu Leu Arg Lys Arg Thr Asp Trp Ala Ser Ala Phe Ile His Ser
50 55 60

Phe Ile Cys Ser Gln Thr Cys Ile Glu His Leu Glu Trp Ser Pro Val
65 70 75 80

Cys Ile Leu Val Arg Leu Asp Gly Ser Arg Asp Phe Leu Pro Leu Arg
85 90 95

Ser Leu Gln Asn Pro Gly Arg Glu Ile Phe Pro His Ile Val Thr Val
100 105 110



BNSDOCID <WO__0162924A2_I_>

Cys Pro Pro Gly Glu Leu Leu Thr Trp Gly Lys Glu Pro Gly Lys Met
115 120 125

Cys Leu Ser Cys Ala Cys Leu Asp Val Thr Ser Ser Val Arg Ser Gln
130 135 140

Glu Lys Val Ala Arg Cys Arg Arg Gln Val Ala Arg Ile Leu Leu Phe
145 150 155 160

Glu Pro Ser Val Met Arg Arg Gln Met Cys Asp Val His Phe Leu Cys
165 170 175

Leu Phe Leu Phe Phe Phe Asn Lys Asn Val Val Phe Asp Cys Arg Asn
180 185 190

Lys Ala Ser Ile Ile Lys Phe Ala Cys Met Leu Asn Glu Ser Met Cys
195 200 205

<210> 120
<211> 179
<212> PRT
<213> Homo sapiens

<400> 120

Thr Gly Pro Thr Pro Asp Gly Pro Pro Ala Pro Val Ala Val Ser Met
1 5 10 15

Leu Ser Thr Ser Pro Cys Ala Ser Ile Leu Gly Leu Cys Leu Cys Ser
20 25 30

Gln His Arg Cys Val Leu Ser Thr Ala Glu Ile Arg Thr Phe Thr Ile
35 40 45

Pro Pro Ala Ala Ser Gly Ala Pro Leu Cys Ser Gly His Leu Thr Leu
50 55 60

Leu Gly Pro Pro His His Cys Thr His His Thr Pro Asn Ser Pro Ala
65 70 75 80

Pro Pro Pro Gly Arg Gly Ser Val Pro Glu Ser Tyr Asp Leu Gly Thr
85 90 95

Pro Ser Pro Ser Leu Gly Trp Leu Leu Leu Leu Pro Gly Leu Val Leu
100 105 110

Gly Ser Thr Thr Tyr Glu Ser Ala Arg Leu Ser Ala Val Ser Thr Cys
115 120 125

Val Ser Val Ser Gly Gly Gly Gly Gly Arg Cys Leu Ser His Ile Pro
130 135 140

Ser Thr Ser His Pro Ser His Ser Ala Ala Thr Ala Gln Ile Gly Leu
145 150 155 160

Leu Val Glu Arg Met Gly Lys Cys Leu Thr His Pro Gly Pro Leu Arg
165 170 175

Val Ala Asn



BNSDOCID <WO 0162924A2 I >

<210> 121
<211> 233
<212> PRT
<213> Homo sapiens

<400> 121

Lys Ser His Thr Ala Leu Leu Pro Tyr Ser His Val Arg Ser Lys Leu
1 5 10 15

Ile Arg Ser Ala Leu Arg Gly Asn Ala Pro Pro Thr Glu Arg Asn Ile
20 25 30

Lys Tyr Phe Val Asp Ile Phe Leu Thr Pro Pro Pro Val Ser Tyr Gln
35 40 45

Ile Asn Ser Ser Lys Cys Leu Asn Thr His Lys Thr Arg His Phe Leu
50 55 60

Tyr Ala Ser Val Val Phe Leu His Leu Lys Cys Ile Met Ser Ile Lys
65 70 75 80

Asn Leu Tyr Glu Val Ala Tyr Ile Glu Ser Val Tyr Ile Gln Cys Gln
85 90 95

Ser Ser Val Ser Ser Ile Ser Phe Arg Ser Arg Lys Lys Thr Val Pro
100 105 110

Asp Ile Tyr Ile Cys Asn Leu Ala Val Ala Asp Leu Val His Ile Val
115 120 125

Gly Met Pro Phe Leu Ile His Gln Trp Ala Arg Gly Gly Glu Trp Val
130 135 140

Phe Gly Gly Pro Leu Cys Thr Ile Ile Thr Ser Leu Asp Thr Cys Asn
145 150 155 160

Gln Phe Ala Cys Ser Ala Ile Met Thr Val Met Ser Val Asp Arg Val
165 170 175

Lys Asp Phe Glu Ile Ser Tyr Asn Ser Glu Val Pro Val Leu Pro Gln
180 185 190

Ala His Ser Asn Ser Asn Thr Ser Phe Gly Leu Gln Gln Arg Phe Ser
195 200 205

Ser Phe Val Ser Leu Asn Leu Leu Lys Asn Ile Leu Phe Asn Phe Thr
210 215 220

Glu Glu Tyr Phe Trp Lys Thr Asn Thr
225 230

<210> 122
<211> 223
<212> PRT
<213> Homo sapiens



BNSDOCID <WO 0162924A2 I >

<400> 122

Leu Thr Glu Gly Leu Glu Tyr Ile Ser Lys Tyr Arg Tyr Lys Asn Lys
1 5 10 15

Phe Leu Leu Leu Gly Ile Tyr His Asn Gly Phe Gln Leu Ser His Leu
20 25 30

Ile Ile Arg Asn Lys Ser Ser His Leu Gly Ala Ile Ile Ser Leu Tyr
35 40 45

Ile Thr Glu Val Trp Asn Arg Thr Gln Ser Leu Pro Asp Phe Leu Ile
50 55 60

Leu Ser Leu Met Gln Thr Gln Thr Val Asn Met Tyr Leu Pro Ser Ala
65 70 75 80

Lys Leu Pro Asn Ser Trp Leu Val Ser Gly Lys Arg Gln Ser Cys Phe
85 90 95

Ser Phe Cys Leu Ser Tyr Asn Leu Glu Thr Leu Lys Lys Leu Ser Ala
100 105 110

Tyr Pro Val Ser Arg Ile Leu Gln Asn Leu Gln Gly Asn Thr Leu Thr
115 120 125

Glu Leu Phe Leu Leu Phe Leu Ile Leu Pro Leu Met Ala Leu Val Val
130 135 140

Val Tyr Gly His Val Ala Lys Lys Leu Trp Ile His Asn Ala Val Asp
145 150 155 160

Asp Ile Ser Ile His Thr Tyr Ile Trp Gln His Gly Glu Lys Lys Glu
165 170 175

Thr Leu Lys Met Leu Met Thr Met Val Leu Val Tyr Thr Ile Ser Trp
180 185 190

Leu Pro Leu Asn Leu Tyr Leu Val Leu Pro Cys Arg Glu Phe Ile Ser
195 200 205

Ser His Asn Gly Leu Cys Phe Phe Phe His Trp Leu Ala Ile Ser
210 215 220

<210> 123
<211> 195
<212> PRT
<213> Homo sapiens

<400> 123

Phe Ile Thr Ala Gln Glu Val Glu Thr Ala Pro Ser Arg Ile Lys Ile
1 5 10 15

Tyr Tyr Ile Lys Pro Asn Lys Arg Asp Tyr Arg His His Ile Ser Ile
20 25 30

Gln Pro Lys Ser Ser Ser Cys Ser Gln Ile Lys Lys Lys Asn Ser Lys
35 40 45



BNSDOCID <WO 0162924A2 I >

Cys Leu Thr Met Asp Asp Tyr Ser Arg Arg Ala Val Glu Gly Cys Leu
50 55 60

Ser Ser Ser Ala Gln Thr Ser Asp Arg Ala Thr Asn Thr Ala Ser Pro
65 70 75 80

Pro Ala Glu Val Glu Val Gln Ala Met Arg Gly Gly Gly Gln Gly Tyr
85 90 95

Phe Leu Ala Leu Ser His Pro Thr Leu Met Pro Val Pro Ala Leu Ser
100 105 110

Thr Leu Glu Ser Tyr Ala Ile Gln Gly Val Asp Glu Val Phe Asn Gln
115 120 125

Glu Lys Ile Leu Pro Cys Pro Pro Ile Glu Glu Ile Glu Asn Glu Ala
130 135 140

Ile Val Gly Val Ile Ser Asn Phe Trp Thr Ser Ala Cys Thr Leu Gly
145 150 155 160

Val Glu Val Glu Lys Asn Tyr Lys Lys Thr Glu Arg Ser Gly Gly Asp
165 170 175

Leu Gly Leu Asp Glu Ile Val Tyr Ile Lys Gly Glu Asn Leu Ile Thr
180 185 190

Leu Pro Leu
195

<210> 124
<211> 188
<212> PRT
<213> Homo sapiens

<400> 124

Phe Met Thr Leu Lys His Leu Ala Asn Leu Ile Ser Asp Leu His Asn
1 5 10 15

Leu Val Met Phe Leu Ser Ile Leu Phe Glu Ala Val Phe Ile Ser Gln
20 25 30

Arg Leu Leu Lys Leu His Lys Leu Lys Gly Ile Thr Val Phe Ile Leu
35 40 45

Leu Ser Arg Tyr Leu Ser Val Tyr Phe Cys Leu Ser Gln Leu Ile Thr
50 55 60

Ala Leu Leu His Lys His Tyr Pro Gln Tyr Ile Tyr Ser Tyr Thr Glu
65 70 75 80

Arg Gln Lys Lys Ile Thr Ala Val Ile Ala Arg Phe Phe Ile Cys Gln
85 90 95

Phe Leu Ser Phe Leu Ile Gly Leu Leu Ala Leu Gly Trp Ser Pro Trp
100 105 110



BNSDOCID <WO__0162924A2_I_>

Lys Ser Arg Ala Arg Lys Gly Val Ser Gly Ala Ser Cys Phe Ser Gln
115 120 125

Gly Ala Gln Ala Leu Arg Ala Ser Ile Ser Ala Phe Asn Thr Asp Phe
130 135 140

Pro His Ser Leu Ile Lys Val Leu Leu Glu Phe Leu Met Pro Asn Ser
145 150 155 160

Gln Tyr Phe Trp Phe Leu Asn Phe Ile Lys Gly Asn Leu Pro Gly Ala
165 170 175

Arg Arg Lys Ile Asp Ser Pro Arg Arg Arg Arg Glu
180 185

<210> 125
<211> 172
<212> PRT
<213> Homo sapiens

<400> 125

Phe His Tyr Arg Ala Tyr Leu Asn Gly Phe Glu Gly Gln Asn Gln Val
1 5 10 15

Met Trp Val Asp Glu Pro Gln Gly Ile Gln Glu Glu Gly Gln Leu His
20 25 30

Leu His Leu Leu Val Ile Arg Gln Ser Ser Ile Gln Glu Ser Ser Gly
35 40 45

Ser Gln Asn Leu Asn Gly Ser Phe Val Gln Tyr Ala Phe Val Ser Phe
50 55 60

Lys Ile Glu Val Ser Lys Val Leu Ala Gly Gln Asn Val Cys Phe Ile
65 70 75 80

Leu Tyr Ser Leu Leu Trp Val Val Val Ile His Leu Phe Ile Phe Ala
85 90 95

Phe Cys Ser Ser Phe Pro Pro Ser Ile His Leu Ser Ile Tyr Leu Leu
100 105 110

Ile Tyr Pro Glu Ile Phe Ile Glu Cys Tyr Leu Cys Ala Gly Ser Tyr
115 120 125

Ser Arg Cys Ser Leu Asn Pro Cys Ile Asn Glu Ala Ser Thr Lys Leu
130 135 140

His Pro Tyr Ile Ala Met Tyr Ile Asp Met Ser Gly Ile Gln Asn Thr
145 150 155 160

Glu Tyr Leu Tyr Lys Leu His Ser Asp Phe Thr Thr
165 170

<210> 126
<211> 89
<212> PRT
<213> Homo sapiens



BNSDOCID <WO 0162924A2 I >

<400> 126

Arg Arg Val Cys Gly Glu Arg Gly Ser Gly Trp Pro Arg Gln His Val
1               5                   10                  15

Ser Ser Thr His Arg Leu Trp Asp Asp Asp Pro His Phe Met Tyr Phe
            20                  25                  30

Pro Arg Ile Glu Lys Tyr Gly Ile Ile Leu Gln Leu Ile Val Trp Leu
        35                  40                  45

Ile Thr Gln Arg Leu Leu Gln Pro Leu Ser Pro His Gln Thr Arg Thr
    50                  55                  60

Val Lys Glu Asn Lys Thr Thr Thr Cys His Gly Asn Thr His Leu Tyr
65                  70                  75                  80

Thr Tyr Ile Ile Phe Lys Asn Leu Ala
                85

<210> 127
<211> 201
<212> PRT
<213> Homo sapiens

<400> 127

Leu Ser Gly Phe Leu Trp Phe Leu Val Leu Gly Leu Pro Thr Leu Ser
1               5                   10                  15

Lys Cys Ile Gly Leu Tyr Leu Tyr Leu Thr Phe Phe Met Leu Phe Pro
            20                  25                  30

Gly Val Val Trp Ile Phe Cys Phe Ile Gln Leu Leu Gln Asn Leu Cys
        35                  40                  45

His Gly Asn Ile Gln Arg Leu Phe Arg His Ser Val Arg Ala Ser Thr
    50                  55                  60

Asp Lys Pro Ser Gly Tyr Ile Gln Thr Met Lys Pro Thr Val Ser Ser
65                  70                  75                  80

Gly Ser Asp Val Ile Leu His Leu Thr Val Leu Leu Phe Asn Arg Val
                85                  90                  95

His Leu Leu Lys Leu Ser Leu Tyr Arg Ile Cys Asn Gly Ile Asp Glu
            100                 105                 110

Ile Asp Ser Gly Asn Ile Gln Leu Ala Val Lys Ser Val Lys Ser Val
        115                 120                 125

Leu Cys Ile Ser Gly Phe Cys Ile Lys Phe Arg Leu Lys Ile Gln Cys
    130                 135                 140

Ser Trp Asp Val Lys Pro Ala Tyr Met Glu Gly Gln Leu Phe Ile Tyr
145                 150                 155                 160

Met Gly Ser Ala Gly Pro Thr Leu Lys Phe Glu Tyr Val Trp Ile Leu



BNSDOCID <WO__0162924A2_I >

165 170 175

Val Ser Met Gly Ile Leu Glu Pro Val Pro Gln Gly Ile Leu Glu Gly
180 185 190

Gln Leu Tyr Asn Ile Leu Leu Leu Leu
195 200

<210> 128
<211> 177
<212> PRT
<213> Homo sapiens

<400> 128

Asp Tyr His Ser Tyr Phe Phe Pro Tyr Ile Arg Ala Gln Pro Leu Leu
1 5 10 15

Cys Leu Gly Leu Pro Val Ile Ile Val Val Val Ser Phe Ile Val Leu
20 25 30

Thr Phe Ser Ser Ser Ser Phe Ile Leu Pro Leu Pro Ser Val Phe Tyr
35 40 45

Asp Gln Ile Gln Ser Leu Lys Thr His Arg Ala His Gln Asn Thr Thr
50 55 60

Leu Gln Pro Asp Ile Gln Ser Cys Pro Val Tyr Arg Ser Asn Phe Phe
65 70 75 80

Ser Ile Tyr Leu Ser Leu Ser Pro His Leu Leu Leu Ile Asn Thr Trp
85 90 95

Ile Leu Tyr Ala Gln Glu Ala Lys Leu Phe Thr Val His Phe Arg Cys
100 105 110

Pro Ser Tyr Phe Pro Phe Ser Ile Leu Leu Thr Met Leu Phe Pro Met
115 120 125

Leu Gly Met Leu Ser Phe Gln His Leu Ser Thr Thr Asn Phe Ala Lys
130 135 140

Tyr Arg Pro Pro Gln Asn Pro Ser Phe Ser Leu Gly Leu Pro Gln Gly
145 150 155 160

Pro Ser Asp Asn Asn Val Pro Ser Pro Ser Phe Cys Ile Ser Cys Ile
165 170 175

His

<210> 129
<211> 206
<212> PRT
<213> Homo sapiens

<400> 129

Met Thr Phe Ser Gly Tyr Ala Gln Asn Lys His Phe Arg Tyr Phe Leu



BNSDOCID <WO 0162924A2 I >

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1               5                   10                  15

Phe Phe Glu Tyr Lys Asn Phe Leu Asp Tyr Val Leu Phe His Leu Ile
            20                  25                  30

Lys Ser Leu Arg Pro Asn Leu Phe Arg Tyr Ile Cys Cys Ile Tyr His
        35                  40                  45

Leu Ile Ser Leu Lys Leu Cys Cys Leu Gln Lys Leu Leu Ala Gly Thr
    50                  55                  60

Ser Val Tyr Asn Ile Leu Ser Ser Thr Leu Thr Ile Ser Ser Ala Pro
65                  70                  75                  80

Lys Gln Gly Leu Gly Leu Pro Phe Gln Glu Tyr Phe Tyr Tyr Ile Tyr
                85                  90                  95

Cys Arg Gln His Arg Thr Leu Ser Lys Cys Leu Leu Ile Ser Pro Val
            100                 105                 110

Lys Ala Ser His Ser Tyr Leu Tyr Ser Ile Gln Tyr Lys Ile Phe Lys
        115                 120                 125

Thr Tyr Gly Gln Asn Lys Arg Ser Thr Ile Leu Thr Lys Leu Asn Leu
    130                 135                 140

Tyr Val Tyr Phe Leu Tyr Leu Tyr Thr Phe Thr Cys Leu Leu Glu Asp
145                 150                 155                 160

Thr Val Asn Thr Asp Asn Phe Lys Glu Ala Ser Phe Ser Phe Ile Asn
                165                 170                 175

Glu Asn Asp Met His Lys Tyr Cys Thr Leu Ser Ser Leu His Ala Lys
            180                 185                 190

Thr Ile Met Thr Lys Ile Cys Cys Thr Leu Ser Gln Thr Phe
        195                 200                 205

<210>  130
<211>  225
<212>  PRT
<213>  Homo sapiens

<400>  130

Ala Gln Gln Val Arg Arg Gln Pro Leu Ser Phe Leu Gly Leu Val Ser
1               5                   10                  15

Tyr Gln Pro Leu Ser Leu Gln Gly Val Pro Arg Gln Pro Arg Gln Pro
            20                  25                  30

Thr Met Ala Gln Phe Leu Ser Val Phe Ser Gly Lys Leu Asp Trp Asp
        35                  40                  45

Asn Arg Thr Glu Thr Pro Gly Gln Val Asn Met Ser His Thr Gly Gly
    50                  55                  60

Glu Trp Leu Val Gly Lys Gln Val Val Phe Ile Leu Thr Val Leu Val
65                  70                  75                  80
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BNSDOCID <WO___0162924A2_I_>

Ala Phe Cys Gly Leu Val Gly Asn Gly Val Val Cys Trp Leu Phe Cys
85 90 95

Phe Gln Val Arg Ser Ser Pro Tyr Val Thr Tyr Val Leu Asn Leu Ala
100 105 110

Ala Ala Asp Met Val Asn Leu Ser Cys Val Thr Val Ile Leu Leu Glu
115 120 125

Lys Ile Leu Met Leu Tyr His Gln Val Thr Leu Gln Val Ala Met Phe
130 135 140

Leu Glu Pro Val Ser Tyr Phe Ser Asp Thr Val Ser Leu Cys Leu Leu
145 150 155 160

Val Ala Met Asn Ile Glu Ser Phe Leu Cys Val Leu Cys Pro Thr Trp
165 170 175

Cys Cys His Arg Pro Lys His Thr Ser Ala Val Met Ser Ile Leu Ser
180 185 190

Trp Ala Leu Ala Leu Ser Phe Ala Cys Gly Pro Gly Leu Val Met Gly
195 200 205

Glu Gly Pro Gly Met Pro Ile Ser Gly Arg Leu Tyr Asn Ile Ser His
210 215 220

Ala
225

<210> 131
<211> 194
<212> PRT
<213> Homo sapiens

<400> 131

Cys Tyr Ile Thr Glu Gln Ser Gly Thr Trp Lys Cys Arg Lys Asp Met
1 5 10 15

Ala Glu Thr Val Ser Ala Phe Glu Gly Phe His Tyr Ser Pro Gly Gly
20 25 30

Lys Met Trp Gly Asp Cys Leu Asn Thr Glu His Pro Val Thr Leu Glu
35 40 45

Phe Trp Ile Asp Thr Asp Phe Phe Phe Leu Glu Ser Lys Tyr Val Ser
50 55 60

Asp Ile Ala Trp Gly Ile Leu Ile Leu Lys Thr Ile Cys Val Val Asn
65 70 75 80

Leu Lys Phe Arg Phe His Trp Val Ser Cys Met Phe Met Cys Ser Ile
85 90 95

Arg Gln Asp Phe Met Gly Lys Ile Lys Leu Ile Ser Tyr Thr Leu Phe
100 105 110



BNSDOCID: <WO__0162924A2_I_>

Leu Phe Leu Asp Pro Arg Ser Ser Leu Cys Ser Pro Phe Leu Leu Leu
115 120 125

Tyr Leu Leu Leu Leu Gly Pro Ser Pro Cys Cys Val His Ser Phe Gln
130 135 140

Asp Met Gln Thr Trp Asp Thr Ala Val Gly Ser Arg Ala Met Tyr Gln
145 150 155 160

Ala Ala Gln Gln Ser Val Lys His Phe Pro Phe Ser Leu Gly Ala Gln
165 170 175

Pro Trp Gly Val Pro Cys Asn Ala Arg Gly Leu Asp Ala Ser Cys Gly
180 185 190

Asn Thr

<210> 132
<211> 163
<212> PRT
<213> Homo sapiens

<400> 132

Gly Glu Trp Cys Leu Val Phe Glu Lys Asn Ser Lys Ser Tyr His Trp
1 5 10 15

Phe Lys Asn Cys Phe Phe Tyr Cys Phe Val His Asp Tyr Leu Glu Gly
20 25 30

Ile Trp Lys Ser Asp Ala Lys Arg Thr Gly Ser Phe Pro Phe Lys Ala
35 40 45

Met Asp Asn Ile Pro Leu Met Lys Met Tyr Ser Cys Ile Gln Ile Cys
50 55 60

Arg Met Val Phe Thr Gln Tyr His Thr Lys His Leu Cys Asn Val Gly
65 70 75 80

Gln Thr Cys Ala Glu His Leu Ala Gln Val Leu Cys Lys Ser Lys Lys
85 90 95

Lys His Trp Met Phe Leu Phe His Leu Lys Glu Ile Lys Ala Thr Val
100 105 110

Leu Tyr Ala Gln Asn Leu Cys Val Ile Asp Arg Leu Thr Ile Gln Ile
115 120 125

Phe Pro Leu Gly Ile Asn Val Lys Ile Met Gln Asn Cys Asn Lys Asn
130 135 140

Phe Lys Met Leu Leu Gly Leu Val Tyr Leu Arg Leu Val Leu Val Phe
145 150 155 160

Cys Thr Asn

<210> 133



BNSDOCID <WO 0162924A2 I >

<211> 152
<212> PRT
<213> Homo sapiens

<400> 133

Leu Phe Leu Phe Tyr Phe Ser Phe Thr Ser Asn Ile Leu Cys Phe Leu
1 5 10 15

Glu Ala Asn Tyr Phe Lys Cys Phe Cys His Pro Leu His Ile Leu Tyr
20 25 30

Lys Ile Glu Asp Lys Ile Ser Asn Tyr Asn Ala Arg Trp Ile Leu Asn
35 40 45

Val Cys Tyr Ser Phe Thr Ile Leu Phe Ser Leu Tyr Met Asn Ile Leu
50 55 60

Ile Gln His Lys Phe Phe Thr Phe Ile Thr Trp Pro Arg Lys Phe Val
65 70 75 80

Leu Lys Ser Leu Val Gln Ile Leu Ile Tyr Asn Lys Thr Tyr Ile Ile
85 90 95

Phe Pro Asn Tyr Tyr Asn Lys Phe Ser Ile Lys Phe Leu Tyr Lys Asp
100 105 110

Asn Tyr Leu Ser Ile Lys Tyr Ser Lys Gln Ile Glu Lys Ser Tyr Lys
115 120 125

Val Ala His Phe Leu Cys Phe Pro Phe Val Phe Val Leu Leu Cys Phe
130 135 140

Val Phe Asp Gly Val Leu Leu Leu
145 150

<210> 134
<211> 165
<212> PRT
<213> Homo sapiens

<400> 134

Ile Asn Val Ala Asn Asn Lys Asn Leu Phe Cys Ser Ser Ser Gly Gly
1 5 10 15

Glu Val Arg Lys Ile Lys Ala Ser Ala Asp Gly Ser Pro Arg Ser Arg
20 25 30

Glu Glu Phe Phe Ile Phe Ser Leu Leu Leu Val Ala Pro Ser Asn Leu
35 40 45

Gly Ile Pro Trp Phe Val Ala Ala Ser Leu Gln Phe Leu Pro Ser Ser
50 55 60

Phe His Glu Leu Ile Ser Cys Val Cys Leu Cys Ile Ser Ser Leu Phe
65 70 75 80

Met Gly Cys Gln Leu Leu Asp Leu Arg Pro Thr Leu Thr Gln Tyr Glu



BNSDOCID <WO 0162924A2 I >

85 90 95

Leu Ile Leu Thr Leu His Leu Gln Arg Pro Tyr Leu Gln Ile Arg Ser
100 105 110

Pro Ser Glu Val Leu Gly Arg His Thr Phe Trp Gly Asp Thr Ile Gln
115 120 125

Leu Ile Thr Pro Gln Leu Pro Lys Leu Glu Arg Ala Asn Thr Glu Asn
130 135 140

His Arg Leu Gln Gly Ala Glu Ala Ser Lys Cys Asn Thr Lys His Leu
145 150 155 160

Asn Asn Asn His Ile
165

<210> 135
<211> 215
<212> PRT
<213> Homo sapiens

<400> 135

Gly Gln Ser Lys Thr Pro Ser Gln Asn Ser Asn Lys Pro Ile Gln Ser
1 5 10 15

Lys Asn Ile Ala Phe Ile Thr Val Tyr Ser Asn Ser Leu His Leu Pro
20 25 30

Val Lys Phe Cys Tyr Phe Pro Tyr Lys Phe Ser Ala Phe Leu Val Lys
35 40 45

Ile His His Arg Tyr Leu Ile Ala Phe Cys Cys Gly Met Met Met Met
50 55 60

Thr Lys Asn Gly Ile Cys Ser Phe Leu Ser Leu Lys Phe Leu Ser Ile
65 70 75 80

Tyr Arg Lys Val Met Gly Phe Phe Ile Phe Thr Ser Ile Trp Phe Arg
85 90 95

Cys Ala Phe Ile Asn Ser Glu Phe Glu Leu Ile Leu Ile Val Phe Tyr
100 105 110

Asn His Thr Ile Lys Leu Tyr Cys Leu Leu Leu Ser Asn Ser Asn Tyr
115 120 125

Ser Glu Gln Thr Ser Leu Thr Tyr Leu Phe Cys Glu Cys Ser Phe Leu
130 135 140

Leu Ala Arg Lys Met Asp Val Cys Ser Ile Asn Ile Leu Ile Glu Tyr
145 150 155 160

Met Ile Thr Cys Ser Ser Leu Gly Glu Ser Leu Phe Leu Ile Leu Ser
165 170 175

Phe Phe Phe Phe Thr Arg Met Ser Phe Lys His Phe Gly Thr Tyr Leu
180 185 190



BNSDOCID <WO___0162924A2 I >

Arg Tyr Phe Phe Phe Lys Val Phe Tyr Ile Ile Leu Glu Phe Leu Asp
195 200 205

Tyr Thr Leu Phe His Pro Cys
210 215

<210> 136
<211> 206
<212> PRT
<213> Homo sapiens

<400> 136

Val Tyr Leu Pro Leu Ser Phe Leu Thr Cys Pro Leu Cys Leu Ile Val
1 5 10 15

Gln Ile Leu Arg Ser Ser Gly Asn Pro Gly Pro Trp Arg Leu Pro Ser
20 25 30

Pro Phe Phe Pro Ala Ser Cys Pro Pro Leu Pro Ile Phe Pro Glu His
35 40 45

Thr Trp Ser Pro Gln Asp Ser Ala Pro Val Tyr Ser Val Phe His Val
50 55 60

Cys Ser Pro Leu Phe Ser Leu Leu Gly Lys Leu Leu Asn Ile Ser Gln
65 70 75 80

Asp Arg Val Leu Ile Ser Leu Arg Met Leu Ser Leu Ala Thr Leu Asn
85 90 95

Val Leu Arg Ala Leu Gly Ser Tyr Leu Cys Glu Ile Thr Ser Leu Thr
100 105 110

Leu His Ile Phe Met Asp Pro Phe Phe Leu Leu Ile Cys Trp Leu Asp
115 120 125

Lys Gly Arg His Tyr Ile His Leu Leu His Leu Trp Ile Ala Arg Val
130 135 140

Gly Ala His Met Phe Leu Leu Asn Val Leu Phe Ile Gln Gly Ala His
145 150 155 160

Val Gln Val Cys Tyr Ile Gly Ile Leu Cys Asp Ala Glu Val Trp Ala
165 170 175

Ser Trp Asp Leu Ile Ala Gln Leu Val Ser Ile Val Pro Glu Arg Phe
180 185 190

Phe Asn Pro Gly Pro Leu Pro Ser Ile Asn Ile Ser Val Thr
195 200 205

<210> 137
<211> 234
<212> PRT
<213> Homo sapiens

<400> 137



BNSDOCID <WO 0162924A2 I >

Tyr Thr Tyr Leu Tyr Ile Asn Ile Ile Phe Ile Tyr Ile Tyr Ile Gln
1 5 10 15

Ile Phe Ile Asn Lys Tyr Val Phe Ile Ile Tyr Leu Tyr Lys Tyr Ile
20 25 30

Phe Ile Tyr Leu Tyr Lys Tyr Leu Tyr Lys Tyr Ile Phe Ile Tyr Leu
35 40 45

Tyr Lys Tyr Val Tyr Lys Asn Ile Asn Ile Phe Ile Ile Tyr Leu Tyr
50 55 60

Lys Tyr Ile Tyr Ile Lys Ile Tyr Leu Tyr Lys Tyr Ile Tyr Ile Lys
65 70 75 80

Ile Tyr Leu Tyr Ile Ile Tyr Leu Tyr Ile Phe Ile Tyr Ile Asn Thr
85 90 95

His Ile His Ala Met Gly Cys Thr Tyr Phe Leu Gly Ser Cys Tyr His
100 105 110

His Phe Cys Tyr Arg Ser Val Gln Leu Pro Leu Leu Met Asp Ser Phe
115 120 125

Ile Gly Tyr Ala Phe Ser Met Val Leu Leu Lys Pro Gly Leu Ser Asn
130 135 140

Ser Val Ser Tyr Leu Asn Ala Glu Lys Lys Arg Thr Ile Thr Leu Ile
145 150 155 160

Pro Ser Val Cys Ile Ile Phe Val Leu Cys Leu Ile Pro Arg Ser Val
165 170 175

Phe Leu Phe Leu Ser Phe Pro His Ile Lys Asn Cys Tyr Val Ser Pro
180 185 190

Leu Leu Ser Leu Leu Asn Pro Ile Trp Leu Trp Phe Lys His His Gln
195 200 205

Arg Ile His Ala Ile Glu Ala His Gly Glu Pro Gln Val Gln Tyr Cys
210 215 220

Leu Ile Ser Gln Asn Leu Cys Val Asn Lys
225 230

<210> 138
<211> 203
<212> PRT
<213> Homo sapiens

<400> 138

Phe Ser Thr Pro Thr Leu Thr Ile Val Thr Ile Phe Ile Val Ser Trp
1 5 10 15

Val Asn Asp Ile Ser Ser Ser Val Ser Ser Ala Phe Met Lys Arg Pro
20 25 30



BNSDOCID <WO 0162924A2 I >

Ala Val Asn Phe Ser Ser Gly Phe Val Leu Thr Ser Leu Arg Asn Leu
35 40 45

Glu Ile Glu Ala Lys Phe Lys Leu Thr Ile Lys Leu Lys Leu Cys Gln
50 55 60

Phe His Phe Lys Trp Ser Pro His His Leu Phe Cys His Tyr Phe Asn
65 70 75 80

Leu Ser His His His Leu Pro Ser Gly Ile His Leu Thr Gly Leu Leu
85 90 95

Phe Cys Phe Leu Cys Cys Pro Ile Tyr Ser Ser His Ser Ser Arg Glu
100 105 110

Leu Leu Lys Ile Ser Leu Leu Cys His Ser His Leu Arg Asn Ser Phe
115 120 125

Val Ser His Cys Thr Tyr Gly Thr Ile Pro Asn Ser Phe Tyr Asn Leu
130 135 140

Arg Asp Pro Ala Ser His Cys Cys Pro Ile Trp Pro Thr Ser Phe Gln
145 150 155 160

Asp Ile Leu Leu His Val His Ala Ala Ala Ala Leu Ala Leu Phe Gln
165 170 175

Phe Leu Lys Gln Ala Gly Leu Phe Pro Ala Ser Glu Pro Ser Asn Met
180 185 190

Ala Thr Phe Leu Cys Leu Glu Cys Cys Tyr Thr
195 200

<210> 139
<211> 132
<212> PRT
<213> Homo sapiens

<400> 139

Phe Ser Trp Leu Met Leu Thr Leu Val Leu Ser Pro Thr Phe Phe Pro
1 5 10 15

Thr Ser Cys Ser His Gln Gly Pro Lys Glu Lys Ile Leu Pro Thr Leu
20 25 30

Val Ala Leu Val Leu Val Pro His Met Val Leu Pro Cys Ala Phe Lys
35 40 45

Val Pro Ser Leu Ala Leu Arg Arg Asp Gly Ile Leu Ala Leu Ser Phe
50 55 60

Cys His Leu Cys Met Glu Thr Gln Val Leu Thr Cys Leu Gly Arg Val
65 70 75 80

Ser Pro Gly Arg Leu Gly Ser Ser Pro Ala Leu Gly Asp Ser Gly Thr
85 90 95

Trp Leu Ala Ala Thr Gln Ala His Trp Pro Ser Gly Ser His Ser Gln



BNSDOCID <WO __0162924A2_I_>

100 105 110

Ser Pro Ser Gln Val Pro Ala Thr His Ala His Ser Ser Ser Leu Pro
115 120 125

Phe Cys Ile Val
130

<210> 140
<211> 203
<212> PRT
<213> Homo sapiens

<400> 140

Ala Arg Pro Gln Thr His Gln Lys Glu Glu Thr Pro Asp Pro Ser Glu
1 5 10 15

His Leu Lys Glu Gln Thr Pro Asp Thr Pro Ser Leu Arg Thr Val Thr
20 25 30

Leu Thr Ala Arg Val His Gly Phe Ile Leu Glu Val Ser Glu Thr Lys
35 40 45

Asn Pro Pro Glu Gly Thr Asn Ser Gly His Ser Ser Thr Ser Leu Lys
50 55 60

Asp Cys Leu Val Ser Asn Asn Pro Cys Lys Ala Ser Met Ala Asp Arg
65 70 75 80

Arg Ile Phe Asn Lys Tyr Leu Gln Leu Leu Ser Ile Asn Gly Ser Ser
85 90 95

Gln Ser Arg Glu Glu Lys Gly Thr Gln Ala Cys Gln Pro Ile Trp Val
100 105 110

Val Leu Cys Gln Val Gln Gly Ile Leu Ile Lys Glu Leu Arg Gly Arg
115 120 125

Arg Leu Cys Arg Glu Lys Met Phe Arg Asn Lys Ser Asp His Phe Gly
130 135 140

Lys Gln Thr Lys Lys Leu Thr Trp Ala Leu His Cys Ser Leu Phe Asn
145 150 155 160

Ala Met Asn Ile Ser Glu Tyr Glu Phe Asp Leu Lys Lys Ile Asn Ser
165 170 175

Gln Val Phe Tyr Gln Asp Leu Arg Thr Thr Met His Leu Thr Ile Gln
180 185 190

Leu Asp Val Val Leu Ser Thr Tyr Ile His Lys
195 200

<210> 141
<211> 176
<212> PRT
<213> Homo sapiens



BNSDOCID: <WO 0162924A2 I >

<400> 141

Ala Pro Ala Val Gly His Gly Arg Pro Pro Leu Val Arg Pro Arg Gln
1 5 10 15

Cys Cys Pro Val Glu Gly Thr Asn Ser Pro Arg Arg Trp Glu Gly Ser
20 25 30

Ala Lys Ile Gln Lys Leu Ile Leu Gln Ser Asn Val Val Cys Leu Leu
35 40 45

Val Leu Phe Tyr Ile Leu Met Val Phe Ser Ile Cys Arg Glu Leu Cys
50 55 60

Ser His His Pro Lys Lys Thr Pro Ala Leu Ile Ser Ser His Ser Ser
65 70 75 80

His Trp Pro Pro Ala Leu Gly Asn His Ser Thr Phe Gln His Cys Glu
85 90 95

Val Ile Asn Ser Gly His Phe Ile Tyr Met Glu Leu Tyr Asn Met Trp
100 105 110

Pro Phe Val Thr Gly Phe Phe Leu Leu Cys Tyr Met Leu Leu Ser Thr
115 120 125

Ile Ser Glu Gln Leu Leu Arg Ser Ile Ile Cys Thr Leu Glu Cys Asn
130 135 140

Ile Phe Leu Leu Asp Val Glu Trp Tyr Asn Glu Ser Val Tyr Ala Cys
145 150 155 160

Glu Ile Leu Leu Lys His Ser Gln Lys Cys Asp Arg His Met Cys Ile
165 170 175

<210> 142
<211> 183
<212> PRT
<213> Homo sapiens

<400> 142

Glu Thr Ser Ser Arg His Gln Gly Val Leu Met Tyr Trp Pro Leu Ile
1 5 10 15

Gln Leu Ile Leu Met Ala Thr Lys Ser Lys Trp Pro Pro Val Thr Val
20 25 30

Ser Leu His Arg Cys Arg Gly Lys Glu Gln Cys Arg Arg Met Arg Pro
35 40 45

Ala Trp Tyr Ser Pro Glu Ala Arg Glu Pro Ala Cys Glu Gly Gly Asp
50 55 60

Ser His Cys Leu Leu Pro His Val Gly Ser Ser Gly Arg Pro Met Lys
65 70 75 80

Arg Gly Pro Gly Trp Ile Met Ala Arg Arg Leu Phe Arg Ala Glu Arg
85 90 95



BNSDOCID <WO _0162924A2 I >

Cys Gln Pro His Arg Ser Glu Lys Glu Thr Gly Val Asn Val Met Gln
100 105 110

Cys Leu Glu Cys Cys Asp Gly Glu Pro Ala Val Glu Ala Leu Gly Phe
115 120 125

Cys Cys Cys Cys Trp Val Ser Phe Cys Phe Tyr Phe Phe Asn Glu Asp
130 135 140

Phe Arg Arg Phe Gln Leu Ser Leu Met Lys Thr Arg Cys Val Gly Ser
145 150 155 160

Trp Val Leu Leu Pro Ala Ala Ala Gly Val Trp Pro Leu Ser Gln Arg
165 170 175

Ala Leu Val Ile Thr Pro Leu
180

<210> 143
<211> 207
<212> PRT
<213> Homo sapiens

<400> 143

Leu Trp Tyr Lys Phe Ala Phe Arg Phe Leu Asp Tyr Arg Ile Leu Phe
1 5 10 15

Gln Arg Leu Lys Met Lys Lys Lys Leu Thr Ile Phe Ser Tyr Ile Glu
20 25 30

Cys Ser Lys Ala His Asp Lys Ile Lys Ser Leu Tyr Asn Thr Glu Cys
35 40 45

Ser Phe Leu Ile Cys Met His Cys Phe Ile Phe Phe Leu Phe Cys Leu
50 55 60

Leu Pro Asn Ile Thr Asn Lys Asn Ala Ile Phe Phe Lys Lys Lys Asp
65 70 75 80

Cys Leu Cys Ser Tyr Gly Cys Met Tyr Phe His Arg Leu Tyr Ile Phe
85 90 95

Asn Leu Arg Glu Phe Val Leu Ile Phe Leu Ser Ile Phe Asn Ser Lys
100 105 110

Leu Ala Ser His Leu Asn Arg Asn Arg Tyr Pro Arg Glu Met Leu Phe
115 120 125

His Glu Val Ser Gly Phe Ser Leu Glu Asp Gln Val Pro Phe Tyr Pro
130 135 140

Leu Leu Arg Lys Met Arg Val Asp Thr Ile Val Gln Gln Ala Arg Tyr
145 150 155 160

Thr Ser Ala Leu Gly Phe Ser Pro Glu Leu Arg Asn Ala His Phe Leu
165 170 175



BNSDOCID <WO 0162924A2 I >

Val Val Phe Leu Lys Ile Ile Ile Ile Val Leu Ile Phe Thr Val Cys
180 185 190

Ile Glu His Ile Phe Gly Val Thr His Gly Lys Cys Tyr Phe Val
195 200 205

<210> 144
<211> 160
<212> PRT
<213> Homo sapiens

<400> 144

Arg Gly Gln Glu Leu Thr Ser Pro Gln Thr Trp Ser Asn Leu Ala Gln
1 5 10 15

Glu Asp Val Cys Ile Pro Arg Arg Ile Gln Cys Glu Val Ser Ile Glu
20 25 30

Gly Glu Val Thr Ala Asp Phe Glu Gly Ile Leu Met Lys Phe Leu Ser
35 40 45

Lys Glu Lys Ile Leu Ala Asp Arg Gln Gln Ser Ile Leu Gln Thr Ile
50 55 60

Phe Trp Gly Phe Asp Glu Ser Ile Leu Ser Ala Lys His Pro Tyr Cys
65 70 75 80

Lys Cys Gln Thr Val Ser Ile Gly Ser Thr Gln Ser Arg His Leu Lys
85 90 95

Leu Trp Met Leu Glu Phe Thr Ala Leu Leu Ile Leu Ser Lys His Thr
100 105 110

Ala Ser Asn Ile Cys Leu Arg Leu Tyr His Lys Arg Gln Asp Lys Phe
115 120 125

Ile Gly His Cys Ser Gln Asn Ile Ser Leu Pro Lys Leu Asn Tyr Val
130 135 140

Ser Gln Glu Ile Glu Ser Asp Pro Leu Val Leu Ala Phe Cys Arg Thr
145 150 155 160

<210> 145
<211> 215
<212> PRT
<213> Homo sapiens

<400> 145

Glu Asp Lys Lys Tyr Glu Asn Phe Asn Ile Ala Asn Met Tyr Leu Ile
1 5 10 15

Leu Leu Lys Leu Leu Phe His Val Phe Gln Lys Ile Tyr Ile Ser Arg
20 25 30

Ile Ala His Ile Glu Ile Ala Val Ile Ile Arg Ala Gln Thr Pro Glu
35 40 45



BNSDOCID <WO 0162924A2 I >

Ser Asp Gln Leu Phe Gln Ala Trp Phe Cys His Leu Leu Val Glu Trp
50 55 60

Arg Ala Cys His Ser Val Cys Leu Ser Leu Phe Pro Tyr Leu Ser Gly
65 70 75 80

Asp Asn Asn Asn Met Tyr Ile Ile Glu Leu Leu Ser Ser Ser Cys Lys
85 90 95

Ser Ile Leu Thr Lys Phe Leu Glu Asn Ala Tyr Ser Lys His Ser Ile
100 105 110

Thr Tyr Ala Ile Cys Ile Ser Ile Asn Arg Tyr Ile Leu Val Val Tyr
115 120 125

Pro Glu Thr Phe Leu Val Cys Ser Leu Leu Pro Phe Phe Phe Pro Glu
130 135 140

Lys Thr His Arg Phe Cys Leu Met His Gly Lys Glu Lys Tyr His Gln
145 150 155 160

Val Leu Gly Ser Ser Lys Lys Ile Lys Lys Pro Lys Thr Cys Thr Leu
165 170 175

Glu Arg Gly Lys Leu Ile Pro Met Glu Lys Lys Lys Lys Arg Asn Leu
180 185 190

Asn Asn Cys Ser Ser Glu Gly His Val Gly Leu Gln Arg Gly Phe His
195 200 205

Met Pro Phe Leu Ser Arg Gly
210 215

<210> 146
<211> 210
<212> PRT
<213> Homo sapiens

<400> 146

Glu Phe Thr Cys Gln Lys Val Ser Ile Phe Asn Ile Ile Leu Phe Phe
1 5 10 15

Lys Tyr Phe Cys Pro Tyr Trp Asn Phe Val Leu Phe Ser Cys Val Met
20 25 30

Ser Leu Phe Val Tyr Val Phe Ile Cys Cys Asn Val Leu Ile Leu Ile
35 40 45

Phe His Phe Leu Phe Lys Leu Thr Leu Gly Gly Cys Trp Val Ile Leu
50 55 60

Met Phe Ile Ile Ile Tyr Phe Ser Trp Thr Phe Leu Thr Asp Lys His
65 70 75 80

Arg Asp Arg Arg Asn Gly Phe Glu Trp Leu Thr Trp Phe Val Gln Asn
85 90 95

Leu Phe Leu Leu Leu Leu Gln Lys Arg Thr Ile Leu Glu Ile Gly Leu



BNSDOCID <WO __0162924A2 I >

100 105 110

Cys Asp Phe Phe Phe Phe Asp Thr Pro Leu Phe Glu Gly Phe Cys Gly
115 120 125

Glu Gly Ser Cys Phe Ser Phe Phe Ser Ser Ser Ser Pro Gln Gly Ile
130 135 140

Pro Pro Phe Leu Arg Ile Phe Pro Leu Pro Gly Ser Ser Thr Val Ser
145 150 155 160

Arg Leu Ser Pro Thr Cys Ser Arg Arg Thr Ser Leu Gln Ser Tyr Phe
165 170 175

Arg Leu Pro Val Gly Asn Ile Ser Ser Gln Val Ser Asp Pro Val Pro
180 185 190

Leu Trp Cys Ser Phe Thr Gln Ala Gly Glu Ile Pro Leu Phe Pro Trp
195 200 205

Asp Glu
210

<210> 147
<211> 168
<212> PRT
<213> Homo sapiens

<400> 147

Lys Asn Gln Glu Val Leu Asp Gln His Ile Lys Pro Val Leu Phe Val
1 5 10 15

Glu Asp Tyr Thr Phe Val Cys Asp Lys Thr Tyr Leu Ser Glu Leu Ser
20 25 30

Gly Trp Ile Asn Leu Leu Ile Pro Ser Ser Ser Phe Asp Val Met Pro
35 40 45

Asp Thr Asn Ser Thr Ile Asn Leu Ser Leu Ser Thr Arg Val Thr Leu
50 55 60

Ala Phe Phe Met Ser Leu Val Ala Phe Ala Ile Met Leu Gly Asn Ala
65 70 75 80

Leu Val Ile Leu Ala Phe Val Val Asp Lys Asn Leu Arg His Arg Ser
85 90 95

Ser Tyr Phe Phe Leu Asn Leu Ala Ile Ser Asp Phe Phe Val Gly Lys
100 105 110

Leu Tyr Val Phe Ile Asp Ser Leu Phe Arg Phe Phe Ile Ser Lys Ser
115 120 125

Leu Lys Ala Phe Val Ile Ser Gly Asp Cys Ile Gln Leu Gly Lys Asn
130 135 140

Lys His Lys Lys Phe Lys Tyr Ile Leu Glu Gly Ala Ile Trp His Cys
145 150 155 160



BNSDOCID <WO 0162924A2 I >

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Lys Gly Met Leu Tyr Ile Cys Lys
                165

<210>  148
<211>  177
<212>  PRT
<213>  Homo sapiens

<400>  148

Lys Ser Lys Ile Gln Asp Asn His Asp Leu Pro Pro Ser Thr Thr Leu
1               5                   10                  15

Lys Val Ile Leu Cys Leu Leu Ile Leu Leu Asn Thr Met Ser Gln Phe
            20                  25                  30

Asn Val Val His Lys Ala Ile His Asn Leu Asn Ser Ile Leu Ser Leu
        35                  40                  45

His Ser Pro Thr Phe Arg Leu Cys Pro Gly Pro Arg Tyr Pro Phe Ile
    50                  55                  60

Ser Leu Pro Thr Leu His Ile Leu Ser His Pro His Ser Leu Asp Val
65                  70                  75                  80

Leu Phe Asn Leu Ser Ser Pro Ser Ile Cys Thr Ser Cys Gln Thr His
                85                  90                  95

Ile Leu Ser Ser Pro Glu Leu Ile Phe Ile Leu Glu Asp Leu Ile Gln
            100                 105                 110

Val Phe Ser Pro Leu Gly Ala Phe Tyr Lys Pro Ser Phe Leu Cys Ser
        115                 120                 125

Asn Leu Gly Ser Ala Val Pro Ser Ile Leu Ser Ser Thr Ile Ala Ala
    130                 135                 140

Pro Thr Ser Ile Ile Asp Leu Ser Tyr Leu Val Val Ile Asn Cys Met
145                 150                 155                 160

Phe Ile Asn Asn Asp Ser Asn Asp Asn Phe Gly Ile Cys Arg Leu Asn
                165                 170                 175

Ile


<210>  149
<211>  122
<212>  PRT
<213>  Homo sapiens

<400>  149

Ser Ser Asn Lys Asn Ser Ser Lys Arg Gly Asp Arg Gly Leu Lys Ile
1               5                   10                  15

Leu Asn Lys Val Gln Thr Leu Leu Val Ile Leu Lys Phe Arg Cys Val
            20                  25                  30
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BNSDOCID <WO 0162924A2 I >

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Asn Leu Ser Lys Val Leu Val Ser Pro Asp Lys Cys Glu Val Asn Glu
        35                  40                  45

Glu Ser Trp Ala Val Leu Ser Lys Cys Leu Gly Ser Phe Gln Lys Pro
    50                  55                  60

Ile Ser Trp Val Lys Cys Ile Asn Val Trp Leu Cys Asp Ile His Phe
65                  70                  75                  80

Asn Val Val Asp Ser Phe Gly Gln Arg Ile Leu Ala Phe Pro Ser Leu
                85                  90                  95

Tyr Met Tyr Pro Leu Ser Ser Thr Ile Ile Asn Phe Leu Asn Gln Leu
            100                 105                 110

Pro Ile Gln Lys Thr Asn Lys Gln Thr Asn
        115                 120

<210>  150
<211>  144
<212>  PRT
<213>  Homo sapiens

<400>  150

Phe Phe Ser Phe Pro Leu Cys Ser Ser Leu Arg Phe Ile Leu Gly Gln
1               5                   10                  15

Leu Ile Ile Lys His Leu Gln Met Gln Met Tyr Asn Ile Ile Ile Asn
            20                  25                  30

Thr Phe Thr Tyr Pro Ala Leu His Leu Thr Cys Thr Phe Ser His Arg
        35                  40                  45

Phe Phe Glu His Met Ile Leu Gln Arg Pro Leu Thr Leu Phe Glu Cys
    50                  55                  60

Asn Val Phe Ile Ser Asp Thr Ile Tyr Ile Cys Leu Tyr Ile Leu Cys
65                  70                  75                  80

Asn Trp Phe Asn Val His His Val Gly Cys Glu Leu Phe Val Phe Leu
                85                  90                  95

Trp His Thr Val Thr Thr Ile Val Leu Ile Asp Asp Leu Cys Leu Asn
            100                 105                 110

Val Asp Arg Phe Leu Ala Asn Gln Ala Ile Val Tyr Thr Lys His Leu
        115                 120                 125

Val Phe Pro Thr Pro His Leu Leu Pro Phe Phe Phe Phe Phe Phe Phe
    130                 135                 140

<210>  151
<211>  133
<212>  PRT
<213>  Homo sapiens

<400>  151
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BNSDOCID <WO 0162924A2 I >

Pro Pro Ala Pro Val Ala Val Ser Met Leu Ser Thr Ser Pro Cys Ala
1 5 10 15

Ser Ile Leu Gly Leu Cys Leu Cys Ser Gln His Arg Cys Val Leu Ser
20 25 30

Thr Ala Glu Ile Arg Thr Phe Thr Ile Pro Pro Ala Ala Ser Gly Ala
35 40 45

Pro Leu Cys Ser Gly His Leu Thr Leu Leu Gly Pro Pro His His Cys
50 55 60

Thr His His Thr Pro Asn Ser Pro Ala Pro Pro Pro Gly Arg Gly Ser
65 70 75 80

Val Pro Glu Ser Tyr Asp Leu Gly Thr Pro Ser Pro Ser Leu Gly Trp
85 90 95

Leu Leu Leu Leu Pro Gly Leu Val Leu Gly Ser Thr Thr Tyr Glu Ser
100 105 110

Ala Arg Leu Ser Ala Val Ser Thr Cys Val Ser Val Ser Gly Gly Gly
115 120 125

Gly Gly Glu Val Ser
130

<210> 152
<211> 196
<212> PRT
<213> Homo sapiens

<400> 152

Thr Lys Phe Ile Pro Gly Met Leu Thr Lys Asn Phe Ser Arg Lys Ile
1 5 10 15

Ile Pro Arg Val Gly Leu Ile Arg Glu Leu Lys Val Gly Arg Asn Lys
20 25 30

Val Val Leu Ser Lys Leu Leu Pro Lys Lys Phe Arg Lys Ser Ala Val
35 40 45

Lys Gln Met Ser Ala Tyr Phe Leu Phe Gln Lys Met Asn Glu Ala Leu
50 55 60

Asp Ser His Ile Leu Ser Phe Ala Val Phe Gln Asp Ala Val Leu Phe
65 70 75 80

Phe Ile Gly Met Leu Ile Gln Lys Phe Val Trp Glu Asn Ser Gln Lys
85 90 95

Thr Leu Phe Val Glu Phe Leu Phe Ile Ser Lys Lys Val Leu Leu Ser
100 105 110

Val Val Phe Ile Gln His Leu Ile Phe Ile His Cys Phe Ser Cys Thr
115 120 125



BNSDOCID <WO_0162924A2_I_>

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Gly Gly Asn Lys Glu Arg Met Gly Leu Val Asp Leu Ser Leu His Ser
    130                 135                 140

Lys Arg Gly Asn Thr Ile Arg Tyr Ser Ser Ile Leu Tyr Val Asp Ile
145                 150                 155                 160

Cys Asn Cys Cys Val Tyr Val Ser Leu Leu Glu Asn Ile Phe Leu Gln
                165                 170                 175

Leu Ser Tyr Trp Val Thr Lys Phe Thr Pro Leu Asn Tyr Glu Lys Ser
            180                 185                 190

Leu Pro Phe Tyr
        195

<210>  153
<211>  150
<212>  PRT
<213>  Homo sapiens

<400>  153

Ile Ile Tyr Leu Leu Tyr His Leu Ile Phe Asn Trp Ser Val Ser Val
1               5                   10                  15

Leu Phe Ser Pro His Leu Phe Pro Leu Met Tyr Asn Gly Ser Leu Leu
            20                  25                  30

Thr Asp Ile Lys Phe Thr Tyr Ser Phe Leu Cys Tyr Leu Phe Leu Leu
        35                  40                  45

Asp Leu Cys His Val Tyr Ser Leu Lys Leu Leu Val Pro Ile Met Tyr
    50                  55                  60

Ile Ser Val Ile Lys Leu Pro Phe Cys Ser Phe Tyr Phe Leu Cys Leu
65                  70                  75                  80

Ile Arg Phe Tyr Ile Ser Leu Leu Ile Thr Gly Ile Phe Cys Phe Thr
                85                  90                  95

Phe Phe Arg Ile Ile Ile Gly Ala Val Phe Lys Ile Ile Ala Cys Phe
            100                 105                 110

Gln Asp Leu Phe His Leu Gly Thr Asp Leu Val Phe Cys Phe Leu Lys
        115                 120                 125

Cys Leu Pro Phe Phe Tyr Met Ser Arg Asn Phe Glu Leu Tyr Ser Glu
    130                 135                 140

His Ser Asn Tyr Val Val
145                 150

<210>  154
<211>  188
<212>  PRT
<213>  Homo sapiens

<400>  154
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BNSDOCID <WO 0162924A2 I >

His Cys Ile Pro Ile Leu Ala Gln Thr Val Phe Trp Ser Pro Ile Tyr
1 5 10 15

His Pro Phe Ser Val Val Leu Val Leu Val Phe Ala Ile Cys Trp Ala
20 25 30

Pro Phe His Ile Asp Arg Leu Phe Phe Ser Phe Val Glu Glu Trp Ser
35 40 45

Glu Ser Leu Ala Ala Val Phe Asn Leu Val His Val Val Ser Gly Lys
50 55 60

Thr Leu Ala Gly Phe Gly Ala Leu Val Phe Arg Gln His Leu Leu Leu
65 70 75 80

His Leu Ala Met Pro Lys Tyr Ser Asn Leu Ser Arg Gly Ser Ala Met
85 90 95

Leu Arg His Leu Ile Phe Leu Leu Phe Arg Asp Leu Cys Leu Ile Leu
100 105 110

Phe Gln Ile His Ile Tyr Gln Ile Thr Ile Phe Lys Ala Thr Leu Trp
115 120 125

Lys Thr Ser Ser Leu Thr Val Met Ile Thr Glu Gly Lys Trp Ser Arg
130 135 140

Ser Asp Ser Phe Gly Tyr Pro Pro Asn Gly His Ala Ile Lys Leu Val
145 150 155 160

Leu Ile Thr Pro Met Ser Leu Glu Ile Ser Tyr Cys Leu Trp Glu Val
165 170 175

Leu Tyr Pro His Glu Gly Lys Leu Asn Gly Ile His
180 185

<210> 155
<211> 194
<212> PRT
<213> Homo sapiens

<400> 155

Leu Glu Val Gly Leu Trp Ala Ala Ser Phe Ile Leu Ala Leu Pro Val
1 5 10 15

Trp Val Tyr Ser Lys Val Ile Lys Phe Lys Asp Gly Val Glu Ser Cys
20 25 30

Ala Phe Asp Leu Thr Ser Pro Asp Asp Val Leu Trp Val Val Lys Thr
35 40 45

Glu Lys Arg Val Glu Leu Ser Cys Glu Glu Leu His Ser Pro Cys Gln
50 55 60

His Val Ser Ser Leu Lys Glu Tyr Pro Tyr Gly Ser Ser Ser Arg Gln
65 70 75 80

Tyr Leu His Val Ser Pro His Ile Gln Ser Arg Val Phe Leu Arg Arg



BNSDOCID <WO 0162924A2 I >

85 90 95

Gly Pro Leu Glu Lys Asp Phe Glu Phe Asn His Val Thr Ser Val Asp
100 105 110

Thr Asn Ile Phe Lys His Gly Phe Thr Phe Ile Ala Ala Arg Arg Ser
115 120 125

Gly Asn Ala Ala Ile Lys Gly Gly Lys Glu Phe Pro Glu Ser Leu Arg
130 135 140

Leu His Leu Ile Ser Met Gln Leu Gln Phe Ala Ile Met Ser Pro Ile
145 150 155 160

Lys Thr Cys Ser Ser Pro Thr Pro Ala Pro His Thr Cys Glu Cys Asp
165 170 175

Leu Ile Trp Lys Gly Phe Phe Arg Cys Asn Gln Ala Lys Leu Arg Ala
180 185 190

Cys Trp

<210> 156
<211> 234
<212> PRT
<213> Homo sapiens

<400> 156

Leu Leu Gly Leu Tyr Ile Phe Leu Ser Leu Val Cys Leu Glu Trp Thr
1 5 10 15

Leu Phe Gln Ser Phe Cys Phe Leu Phe Leu Cys His Leu Val Ile Phe
20 25 30

Ile Asp Trp Gly Thr Leu Gly Gly Ser Gly Leu Arg Thr Ser Val His
35 40 45

Gln Gly Thr Leu Ala Gly Gln Glu Arg Ser Glu Pro Trp Gly Arg Ala
50 55 60

Gln Val Lys His Lys Leu Gly Ser Ser Cys Pro His Leu Pro Gly Glu
65 70 75 80

Ile Arg Thr Leu Cys Cys Gly Lys Ala Pro Val Leu Thr Leu Cys Gly
85 90 95

Gly Gly Val Leu Leu Gln Tyr Cys Cys Gly Lys Ala Pro Pro Phe Leu
100 105 110

Val Phe His Ile Gly Leu Ile Tyr Ser Tyr Phe Leu Tyr Leu Phe Cys
115 120 125

Pro Leu Ile Ser Phe Cys Ser His Leu Ile His Phe His Pro Asn Tyr
130 135 140

His Ser Val Leu Tyr Thr Tyr Ser Tyr Ile Ile Ala Ser Leu Ser His
145 150 155 160



BNSDOCID <WO 0162924A2 I >

Lys Leu Trp Tyr Asp Lys Val Met Phe Val His Cys Phe Cys Lys Lys
165 170 175

Ala His Ser Ala Phe Trp Gly Tyr Leu Leu Ile Asn Leu Tyr Arg Ile
180 185 190

Pro Met Arg Ile Gly Leu Asp Arg Val Phe Ser Thr Gln Phe Thr Arg
195 200 205

Pro Cys Cys Leu Ser Ile Met Ile Lys Asp Tyr Tyr Tyr Val Lys Met
210 215 220

Phe Ile His Ile His Lys Phe Val Glu Ile
225 230

<210> 157
<211> 183
<212> PRT
<213> Homo sapiens

<400> 157

His Leu Ile Leu Pro Leu Gly Cys Gln Pro Ala Asp His Arg Met Thr
1 5 10 15

Phe Ser Gly Tyr Ala Gln Asn Lys His Phe Arg Tyr Phe Leu Phe Phe
20 25 30

Glu Tyr Lys Asn Phe Leu Asp Tyr Val Leu Phe His Leu Ile Lys Ser
35 40 45

Leu Arg Pro Asn Leu Phe Arg Tyr Ile Cys Cys Ile Tyr His Leu Ile
50 55 60

Ser Leu Lys Leu Cys Cys Leu Gln Lys Leu Leu Ala Gly Thr Ser Val
65 70 75 80

Tyr Asn Ile Leu Ser Ser Thr Leu Thr Ile Ser Ser Ala Pro Lys Gln
85 90 95

Gly Leu Gly Leu Pro Phe Gln Glu Tyr Phe Tyr Tyr Ile Tyr Cys Arg
100 105 110

Gln His Arg Thr Leu Ser Lys Cys Leu Leu Ile Ser Pro Val Lys Ala
115 120 125

Ser His Ser Tyr Leu Tyr Ser Ile Gln Tyr Lys Ile Phe Lys Thr Tyr
130 135 140

Gly Gln Asn Lys Arg Ser Thr Ile Leu Thr Lys Leu Asn Leu Tyr Val
145 150 155 160

Tyr Phe Leu Tyr Leu Tyr Thr Phe Thr Cys Leu Leu Glu Asp Thr Val
165 170 175

Asn Thr Asp Asn Phe Lys Glu
180



BNSDOCID <WO _ 0162924A2 I >

<210> 158
<211> 149
<212> PRT
<213> Homo sapiens

<400> 158

Lys Ile Ile Gln Asn Ala Cys Gln Ile Ile Leu Thr Ser Leu Pro Cys
1 5 10 15

Trp Cys Phe Trp Ser Ile Asp Cys Phe Phe Ser Phe Lys Leu Ile Leu
20 25 30

Ser Ile Met Ser Asp Phe Leu His Asn Thr Leu Gly Ile Met Phe Asn
35 40 45

Ser Gly Ser Tyr Leu Asn Pro Leu Phe Tyr Val Asp Phe Ser Asp Thr
50 55 60

Thr Leu Ile Gly Val Gly Val Gly Val Thr Val Ser Leu Pro Arg Arg
65 70 75 80

Gly Trp Lys Tyr Ser Phe Pro Thr Pro Val Leu Ile Leu Glu Trp Glu
85 90 95

Ser Ser Leu Gln Leu Gly Gly Ile Gly Ala Thr Ala Pro Cys Trp Val
100 105 110

Pro Thr Tyr Thr Thr Leu Ala Gly Ser Gly Arg Ser Ala Leu Ser Leu
115 120 125

Cys Pro Met Trp Pro Pro Leu Thr Leu Trp Gly Gly Val Ser Leu Leu
130 135 140

Pro Leu Ser Gly Gly
145

<210> 159
<211> 207
<212> PRT
<213> Homo sapiens

<400> 159

Cys Ala Gly Ser Lys Arg Pro Thr Ile Ala Leu Leu Ala Thr Leu Ser
1 5 10 15

Gly Lys Leu Asp Trp Asp Asn Glu Thr Glu Thr Ser Gly His Val Asn
20 25 30

Met Ser His Thr Gly Gly Glu Trp Leu Val Asp Arg Gln Val Val Phe
35 40 45

Ser Leu Thr Val Leu Val Ala Leu Cys Gly Leu Val Gly Asn Asp Val
50 55 60

Ile Cys Trp Leu Leu Tyr Ser Gln Val Trp Ser Ser Pro Tyr Val Thr
65 70 75 80



BNSDOCID <WO__0162924A2 I >

Tyr Ile Leu Asn Leu Ala Thr Val Asp Met Val Asn Leu Ser Cys Val
85 90 95

Thr Val Ile Leu Leu Glu Lys Ile Leu Met Leu Tyr His Gln Ala Ala
100 105 110

Leu Gln Val Ala Val Phe Leu Asp Pro Val Ser Tyr Phe Ser Asp Thr
115 120 125

Val Gly Leu Cys Leu Leu Val Ala Met Ser Ile Glu Ser Phe Leu Cys
130 135 140

Ala Leu Cys Pro Thr Trp Cys Cys His Arg Pro Glu His Thr Ser Ala
145 150 155 160

Met Val Arg Trp Ala Leu Ala Leu Ser Leu Tyr Ala Val Ser Gln Val
165 170 175

Cys Glu Tyr Trp Glu Lys Cys Leu Ala Cys Asp Gln Phe His Glu Ala
180 185 190

Leu His Val Met Tyr Leu Phe Ala Leu Trp Ala Cys Pro Ser Ser
195 200 205

<210> 160
<211> 198
<212> PRT
<213> Homo sapiens

<400> 160

Ile Asn Ile Ser Phe Phe Lys Asn Asn Asn Val Ile Val Tyr His Phe
1 5 10 15

Asp Asn Ile Phe Ile Leu Asn Phe Asn Lys Lys Ala Cys Leu Leu Ile
20 25 30

Phe Leu Ile Asn Tyr Leu Val Phe Lys Tyr Leu Ser Tyr Leu Lys Thr
35 40 45

Asp Ile Ser Ile Thr Lys Ser Thr Ser Asn Ser Lys Pro Gly Arg Lys
50 55 60

Ala Asn Lys Ile Thr Asn Phe Lys Leu Arg Leu Leu Ser Gly Met Cys
65 70 75 80

Leu Cys Leu Leu Leu Phe Thr Val Thr Phe Ala Phe Phe Ser Thr Gln
85 90 95

Phe Thr Ser Glu Leu Gly Met Lys Leu Ile Leu Ala Tyr Phe Phe Pro
100 105 110

Phe Val Phe Val Lys Glu Glu Thr Gln Ser Ile Leu Glu Asn Pro Val
115 120 125

Trp Asn Ile Leu Met Phe Thr Ile Ser Asn Ile Met Lys Tyr Val Thr
130 135 140

Tyr His Leu His Leu Phe Gly Asn Tyr Leu Cys Thr Phe His Phe Asp



BNSDOCID <WO 0162924A2_I_>

145 150 155 160

Thr Gln Lys Trp Pro Leu Phe Phe Leu Cys Met Lys Pro Ile Tyr Tyr
165 170 175

Ile Arg Phe Tyr Ser Ile Ser Lys Leu Phe Gln Ser Ser Phe Ile Gly
180 185 190

Gln Thr Asp Ser Gln Tyr
195

<210> 161
<211> 98
<212> PRT
<213> Homo sapiens

<400> 161

Met Val Glu Ser Val Lys Leu Val Lys Ser Phe Leu Leu Val Leu Gly
1 5 10 15

Thr Phe His Phe Lys Asn Ile Ser Lys Tyr Asn Tyr Ile Cys Pro Ser
20 25 30

Pro Phe Leu Lys Gly Leu Tyr Ile Ile Thr Tyr Ile Leu Phe Tyr Leu
35 40 45

Val Leu Phe Ile Tyr Pro Gly Asp His Phe Gln Ser Ser Val Tyr Ser
50 55 60

Ser Leu Cys Lys Cys Lys Thr Asp Tyr Ser Ala Ser Asn Thr Gly Trp
65 70 75 80

Thr Phe Leu Ser Phe Thr Leu Leu Leu Ile Val Leu Ile Ala Leu Pro
85 90 95

Phe Cys

<210> 162
<211> 185
<212> PRT
<213> Homo sapiens

<400> 162

Arg Arg Ser Pro Pro Ala Gly Thr Ala Ala Ala Ser Ala Gln Pro Thr
1 5 10 15

Trp Glu Gly Gly Ser Leu Ser Gly Ser Phe Asn His Thr Gln Gly Ile
20 25 30

Ala Val Phe Cys Leu Gly Val Arg Glu Ser Ser Pro Trp Ser Trp Gly
35 40 45

Thr Ala Leu Met Ser Glu Glu Asn Leu Ala Leu Gly Val Trp Thr Thr
50 55 60

Cys Val Lys Ile Leu Ala Trp Arg Leu Pro His Cys Val Thr Leu Ser



BNSDOCID <WO 0162924A2 I >

65 70 75 80

Lys Phe Leu Asn Leu Ser Gly Ser Pro Phe Ser Arg Cys Thr Thr Gly
85 90 95

Gly Thr Val Pro Arg Arg Thr Leu Arg Ser Ser Val Gly Gly Glu Trp
100 105 110

Gly Leu Val Trp Ala Arg Arg Gly Leu Ala Ser Gln Ser Pro Glu Leu
115 120 125

Arg Ile Glu Arg Val Phe His Phe Thr Gly Gly Arg Gly Ala Ser Pro
130 135 140

Thr Ser Trp Thr Ser Leu Pro Gly Val Gly Lys Gly Gly Val Gly Ala
145 150 155 160

Val Leu Ser Ser His Thr Trp Thr Asp Ser Ser Thr Pro Tyr Ala Pro
165 170 175

Pro Ser Leu Pro Ser Ser Gly Pro Arg
180 185

<210> 163
<211> 189
<212> PRT
<213> Homo sapiens

<400> 163

Pro Ser Pro Gly Ser Phe Arg Thr Lys Thr Phe Leu His Ser Leu Leu
1 5 10 15

Cys Val Ile Lys Ile Gly Ser Asn Pro Pro Thr His Ser Met Lys Gly
20 25 30

Asn Thr Val Val Lys Asn Leu Lys Phe Phe Ser Val Asn Ser Asn Pro
35 40 45

Gly Trp His Leu Asn Phe Glu Arg Ser Lys Arg Val Asp Leu Ala Val
50 55 60

Tyr Gln Leu Pro Thr Val Leu Ser Asp Pro Trp Lys Phe Leu His Ile
65 70 75 80

Leu Trp Arg Pro Phe Arg Ala Glu Ile Cys Leu Gly Val Cys Gly Thr
85 90 95

Glu His Ser Gly Cys Arg Met Trp Gln Ser Ile Arg Ser Leu Leu Arg
100 105 110

Pro Ser Leu Ser Leu Trp Gly Ser Phe Leu Glu Val Glu Pro Glu Ser
115 120 125

Phe Ser Arg Leu Gly Thr Cys Glu Leu Thr Gly Tyr Leu Arg Thr Val
130 135 140

Glu Ala Asn Lys Glu Ala Gln Glu Ala Ser Glu Val Ser Tyr Ile Ala
145 150 155 160



BNSDOCID <WO 0162924A2 I >

MISSING AT THE TIME OF PUBLICATION



BNSDOCID <WO 0162924A2 I >

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Val Leu Asn Arg Cys Thr Val Ser Ser Gly Thr Ile Glu Leu Leu Phe
        35                  40                  45

Trp Ala Tyr Glu Leu Phe Pro Val Pro Tyr Cys His Pro Ile Phe Ala
    50                  55                  60

Ile Tyr Lys Met Ser Ile Phe Phe Met Gly Val Asp Glu Leu Leu Phe
65                  70                  75                  80

Gly Phe Ile Glu Gly Cys Phe Gly Thr Phe Ile Ser Ala Asn His Gly
                85                  90                  95

His Ala Ser Ile Cys Pro Arg Glu Arg Ala Ser Lys Cys Asn Val Leu
            100                 105                 110

Asp Val Ser Val Lys Ser Pro Gln Glu Ala His Asp Ser Asn His Arg
        115                 120                 125

Gly Ser Gln Gly Pro Ser Arg Thr Gly Thr Ser Gly Leu Ala Cys Gly
    130                 135                 140

Phe Ser Trp Tyr Val Cys Ile Ala
145                 150
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<210> 171
<211> 197
<212> PRT
<213> Homo sapiens

<400> 171

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Gly Gln Val Lys Lys Ser Lys Leu Phe Gly Leu Gln Phe Ser Gln Thr
1               5                   10                  15

Gln Glu Pro Ile Ile Gln Lys Gln Leu Ser Tyr Tyr Leu Phe Leu Leu
            20                  25                  30

Gly Gly Thr Pro His Lys Gln Gly Leu Ala Gly Val Val Phe Val Leu
        35                  40                  45

Tyr Trp Leu Arg Glu Gly Lys Gly Val Phe Leu Ile Val Phe Pro Val
    50                  55                  60

Ala Gln Ile Leu Arg Cys Gly Asn Ala Tyr Cys His Phe Gly Lys Asn
65                  70                  75                  80

Ser Phe Phe Ile Tyr Asn Thr Tyr Val Ile Ile Leu Ile Gln Phe Tyr
                85                  90                  95

Lys Ile Ile Tyr Asn Met Lys Tyr Ile Phe Glu Lys Asn Asn Tyr Leu
            100                 105                 110

Tyr Tyr Leu Tyr Leu Phe Arg Pro Cys Leu Ser Lys Val Leu Leu Ser
        115                 120                 125

Leu Ala Thr Val Tyr Phe Pro Leu Trp Phe Glu Leu Lys Gln Met Leu
    130                 135                 140
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BNSDOCID <WO 0162924A2 I >

Lys Glu Asn Lys Pro Ser Glu Pro Pro Asp Ser Phe Ile Ala Ala Val
145 150 155 160

Tyr Leu Leu Leu Ile Leu Leu Lys Phe Met Leu Gln Gln Ser Lys Thr
165 170 175

Gln Trp Ser Glu Thr Ser Leu Ile Glu Thr Gln Val Phe Leu Val Ser
180 185 190

Pro Leu Asp Arg Ala
195

<210> 172
<211> 174
<212> PRT
<213> Homo sapiens

<400> 172

Lys Gln Asn Leu Glu Ser Val Glu Ala Met Ile Phe Tyr Ser Phe Met
1 5 10 15

Thr Leu Arg Gln Cys Asn His Gly Leu Tyr Leu Ser Tyr Phe Phe Leu
20 25 30

Tyr Ser Met Ile Leu Leu Tyr Trp Val Ile Phe Gly Ser Gln Glu Ser
35 40 45

Met Ala Leu Val Trp Asn Phe His Gly Val His Lys Asn Asp Phe Asn
50 55 60

Gln His Ile Ile Ile Asn His Ile Tyr Ile Gly Ser Arg Tyr Arg Ser
65 70 75 80

Thr Cys Leu Ala His Ser His Ile Ser Val Ser His Gln Ser Ser Thr
85 90 95

Glu Arg Gly Gln Ile Phe Gln Lys Lys Gly Leu Glu Asn His Leu Glu
100 105 110

Gln Val Ala Ser Leu Ile Tyr Asn Leu Gly Asn Arg Ile Gly Glu Pro
115 120 125

Ile Lys Gly Ser Cys Ser Phe Ala Pro Glu Asn Lys Thr Gly Thr Pro
130 135 140

Ala Met Thr Val Lys Tyr His Arg Leu Pro Cys Asn Ser Asp Pro Ser
145 150 155 160

Arg Leu His Leu Trp Gly Ser Leu Arg Thr Arg Gly Phe Gly
165 170

<210> 173
<211> 175
<212> PRT
<213> Homo sapiens

<400> 173



BNSDOCID <WO 0162924A2 I >

Lys Asn Cys Ile Lys Phe Ala Gln Phe Gly Gly Lys Thr Gly Phe Gln
1 5 10 15

Lys Ser Ile Thr Leu Phe Leu Ile Asn Pro Leu Val Ser Gln Ser Phe
20 25 30

Ile Leu Trp Ser Ile Ile Ser Gln Ser Val Pro Ile Arg Lys Thr Lys
35 40 45

Asn Thr Val His His Ser Asn Thr Lys Gly Phe Asn Ser Gly Lys Arg
50 55 60

Leu Gln Arg His Trp Lys Gly Trp Gly Arg Lys Glu Arg Arg Leu Pro
65 70 75 80

Arg Asp Glu Arg Ala Ala Thr Thr Leu Arg Leu Glu Pro Ser Ser Cys
85 90 95

Ile Cys Cys Trp Arg Leu Arg Cys Gly Gln Cys Pro Phe Ser Thr Phe
100 105 110

Thr Glu Glu Ala Leu Cys Gly Gln Cys Arg Ile Gly His Asp Thr Ser
115 120 125

Thr Thr Gly Ala Arg Ser Glu Trp Arg Leu Ser Ser His Gln Leu Ser
130 135 140

Leu Ala Lys Phe Asp Lys Pro Val Gly Lys Gly Phe Trp Gln Met Glu
145 150 155 160

Tyr Thr Gly Phe Gln Ala Leu Gln Leu Asn Arg Val Gln Lys Gly
165 170 175

<210> 174
<211> 193
<212> PRT
<213> Homo sapiens

<400> 174

His Asp Gly Arg Ala Tyr Cys Thr Ser Met Leu Gly Ile Ala Tyr Gly
1 5 10 15

Ser Ala Thr Asn Leu Phe Ser Met Leu Leu Leu Asp Ile Val Gly Asn
20 25 30

Cys Asn Thr Met Val Ser Ile Cys Val Ser Lys Tyr Ile Asn Met Glu
35 40 45

Arg Thr Gln Lys Tyr Ser Ile Ile Ile Ser Trp Asp His His Cys Ile
50 55 60

Ser Gly Ser Leu Thr Lys Thr Leu His Asp Cys Ser Ser Leu Leu Gly
65 70 75 80

Gly Gly Gln Lys Leu Val Arg Asn Gly Trp Gln Leu Glu Gly Lys Glu
85 90 95

Met Thr Gln Ala Leu His Ser Pro Thr Ala Ala Ala His Arg Trp Pro



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100 105 110

Ser Thr Gly Lys Pro Glu Leu Thr Glu Leu Thr Pro Gly Glu His Ser
115 120 125

Leu Ile Gly Phe Ile Ile Ile Ser Gln Ser Lys Thr Glu Leu Trp Leu
130 135 140

Arg Ile Lys Ala Arg Phe Phe Phe Leu Asn Ser Ile Ile Phe Ile Lys
145 150 155 160

Leu Ser Lys Val Ser Leu Gly Lys Thr His Met Ser Gln Ala Phe Ser
165 170 175

Val Ser Arg Gly Lys Arg Leu Phe Gln Lys Gln Lys Glu Glu Phe Ile
180 185 190

Ser

<210> 175
<211> 236
<212> PRT
<213> Homo sapiens

<400> 175

Leu Ser Cys Ser Pro Pro His Pro Gly Thr Pro Asn Pro Ser Pro Cys
1 5 10 15

His Leu Gly Phe Cys Ile Ile Leu Thr Gly Phe Tyr His Thr Phe Ile
20 25 30

Tyr Leu Phe Ile His Phe Leu Cys Leu Leu Ser Ala Phe Cys Leu Ser
35 40 45

His Ser Met Lys Thr Leu Gly Val Ser Met Lys Thr Ala Arg Leu Arg
50 55 60

Ser Leu Leu Glu Ala Gln Trp Thr His Arg Leu Ser Ser Pro Leu Gly
65 70 75 80

Thr His His His Ile His Ile Glu Phe Thr Leu Pro Thr Gly Cys Phe
85 90 95

Gln Pro Ala Ala Glu His Ser Lys Val Ile Asn Thr Asp Pro Phe Gly
100 105 110

Lys Met Gln Asp Ser Leu Met Gly Asp Phe Gly Ser Arg Ile Pro Arg
115 120 125

Trp Trp Gly Gln Ser Ile Pro Gly Ile Ala Leu Gln Pro Lys Ala Val
130 135 140

Leu Leu Gln Ala Ser Ser Leu Pro Cys Leu Leu Leu Gln Ala Ser Asp
145 150 155 160

Leu His His Ser Val Arg Leu Ser Leu Ser Phe Leu Ala Leu Ser Pro
165 170 175



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Gly Asn Val Ile Leu Ser Trp His Leu Leu Leu Ser Gly Thr Gly Leu
180 185 190

Met Tyr Gly Phe Cys Ser Leu Met Tyr Pro Glu Tyr Leu Asp Leu Glu
195 200 205

Val Cys Ser Lys Tyr Leu Trp Lys Glu Arg Leu Met Lys Ala Lys Cys
210 215 220

Lys Pro Ile Ala Phe Ile Leu Gly Ala Ala Pro Arg
225 230 235

<210> 176
<211> 129
<212> PRT
<213> Homo sapiens

<400> 176

Gln Leu Ile Phe Thr His Ala Ile Leu Leu Ser Asp Asp His Phe Asn
1 5 10 15

Ser Ile Lys Trp Lys Gln Asp Asn Val Ser Val Ile Leu Ser Leu Val
20 25 30

Ser Arg Ala Gln Ala Ile Val Phe Thr Met Leu Ser Gln Phe Ser Leu
35 40 45

Pro His Cys Arg Cys Val Leu Arg Gly Ala Val Gly Ser Ile Val Cys
50 55 60

Pro Glu Pro His Val Asn Gly Asn Met Met Val Leu His Cys Glu Arg
65 70 75 80

Arg His Asp Arg His Gly Asn Val Ser Gly Arg Asn Lys Ser Ile Ile
85 90 95

Lys Ile Leu Arg Gln Lys Phe Lys Asn Ser Trp Pro Leu Gly Glu Gly
100 105 110

Leu Ser Phe Ile Lys Asn Ile Phe Met Ile Ile Asn Leu Tyr His Thr
115 120 125

Arg

<210> 177
<211> 185
<212> PRT
<213> Homo sapiens

<400> 177

Leu Leu Val Pro Ser Thr Pro Cys Phe His Gly Cys Gly Val Ile Cys
1 5 10 15

Leu Lys Lys Ser Ser Pro Tyr Pro Ile Trp Leu Thr Ala Ser Ser Leu
20 25 30



BNSDOCID <WO __0162924A2_I >

Ser Gly Phe Ile Leu Ala Phe Ser Met Val Asn Leu Pro Pro Asn Ser
35 40 45

Pro Ser Leu Pro Ser Leu Glu Tyr Ser Ser Pro Ile Leu Leu Trp Tyr
50 55 60

Pro Val Met Pro Leu Ala Asn Tyr Leu Ile Ile Leu Pro Ala Ile Asp
65 70 75 80

Cys Ser Cys His Trp Thr Val Phe Val Leu Leu Leu Met Phe Tyr Pro
85 90 95

Pro Val Pro Asn Thr Val Ser Gly Thr Gln Tyr Val Leu Ser Lys His
100 105 110

Leu Leu Val Ser Ser Asn Ser Leu Ser Val Lys Arg Val Ala Lys Gln
115 120 125

Ile Phe Asn Ile Ser Asp Leu Tyr Phe Phe Val Glu Tyr Ile Val Ala
130 135 140

Arg Glu Glu Cys Thr Pro Leu Gln Lys Ile Tyr Thr Tyr Ile Phe Met
145 150 155 160

Phe Tyr Ile Ile Gln Ser Leu Cys Ser Ile Ser Pro Thr Glu Gln Phe
165 170 175

Lys Ala His Phe Cys Leu Val Ser Glu
180 185

<210> 178
<211> 196
<212> PRT
<213> Homo sapiens

<400> 178

Ala Gly Glu Arg Gly Ser Glu Gln Thr Glu Glu Gly Gly Leu Cys Gly
1 5 10 15

Thr Asp Leu Gly Arg Ala Leu Val Ile Ile Leu Ser Phe Tyr Phe Gly
20 25 30

Lys Ser His Gly Ala Val Thr Leu Ala Val Asn Gly Pro Lys Pro Pro
35 40 45

Leu Ser Ser Ala Gly His Asp Ala Leu Trp Gln Val Cys Leu Gly Leu
50 55 60

Pro Glu Arg Ser Gln Ser Leu Val Phe Phe Ser Ala Thr Tyr Leu Asp
65 70 75 80

Arg Glu Ile Leu Thr His Ser Ala Asp Trp Ala Pro Thr Val Cys Val
85 90 95

Cys Val Arg Arg Phe Leu Val Gly Thr Leu Gly Gly Ser Ala Ser Trp
100 105 110



BNSDOCID <WO 0162924A2 I >

Asp Ala Phe Gly His Leu Cys Val Cys Pro Phe Gly Gly Gly Cys Ala
115 120 125

Gly Thr Leu Leu Pro Leu Gln Val Ser Val Ile Ile Thr Ile Trp Ser
130 135 140

Gly Leu Tyr Cys Glu Trp Pro Arg Val Ala Val Gly His Val Asn Gln
145 150 155 160

Arg Cys Pro Val Val Gly His Trp Trp Glu Glu Gly Trp Asp Glu Cys
165 170 175

Leu Pro Leu Ser Ala Val Arg Cys Val Asn Ile Ser Leu Asn Pro Met
180 185 190

Arg Ser Gly Gly
195

<210> 179
<211> 197
<212> PRT
<213> Homo sapiens

<400> 179

Ser Ala Leu Thr Gln Ser His Leu Ala Met Lys Ile Leu Arg Asn Ser
1 5 10 15

Leu Leu Leu Ser Arg Ala His Leu Thr Gln Ser His His Gln Pro Gln
20 25 30

Glu Gly Val Ala Leu Gly Gly Leu Gly Glu Arg Glu Gly Pro Gly Glu
35 40 45

Arg Thr Ala Gly Leu Lys Pro Leu Arg Arg Glu His Ala Cys Ser Pro
50 55 60

Gly Thr Gly Arg Gly Arg Pro Ala Glu Leu Gln Gln Ala Arg Asn Gln
65 70 75 80

Ala Thr Ala His Pro Gln Glu Gln Asp Asp Trp Lys Gly Ala Arg Gly
85 90 95

Leu Gln Thr Leu Asn Cys Leu Asp Met Trp Leu Lys Ala His Ser Asn
100 105 110

Cys Asn Ala Arg Lys Arg Pro Pro Asp Trp Cys His Leu Gly His Leu
115 120 125

His Asp Lys Leu Ser His His Thr Pro Pro Glu Gln Lys Ala Arg Leu
130 135 140

Leu Cys Pro Val Glu Ala Gly Pro Ser Leu Glu Thr Ser Leu Thr Asp
145 150 155 160

Thr Thr Gly Phe Lys His Gly Leu Leu Pro Arg Phe Ile Trp Leu Cys
165 170 175

Ser Ala Ser Leu Ser His Gly Arg Met Asn Ala Cys Ile Pro Gln Lys



BNSDOCID <WO 0162924A2 I >

180 185 190

Glu Ala Ser Gly Leu
195

<210> 180
<211> 194
<212> PRT
<213> Homo sapiens

<400> 180

Gly Leu Cys Leu Tyr His Leu Pro Gln Pro Thr Ser Ile Gln Leu Met
1 5 10 15

Ala Ala Pro Thr Phe Lys Gln Ser Leu Val Leu Ala Phe Val Trp Leu
20 25 30

Tyr Phe Leu Phe Pro Arg Pro Ser Leu Pro Ser Phe Pro Ala Ser Ser
35 40 45

Leu Lys Ser Gly Gln Thr Ser Lys Ser Gly Cys Ser Ser Val Cys Trp
50 55 60

Val Phe Ser Phe Leu Pro His Leu Ser Thr Pro Phe Leu Trp Val Ile
65 70 75 80

Phe Ser Phe Pro Ala Met Leu Asn Ala Ile Phe Val Leu Thr Ala Pro
85 90 95

Gln Phe Gly Leu Gln Pro Asn Pro Leu Cys His Ile Leu Phe Pro Leu
100 105 110

Ser His Tyr Ala Pro Arg Arg Arg Ile Thr Leu Phe Cys Val Gly Ala
115 120 125

Ser Asp Leu Leu Asn Pro Val Pro Glu Thr Leu Gly Leu Trp Leu Phe
130 135 140

Leu Phe Leu Leu Leu Ser Ser Val Ser Leu Phe Gln Lys Gly Tyr Ile
145 150 155 160

Ser Asp Ser Ser Ser Ser Asn Ile Gly Thr Leu Pro Ile Ile Leu His
165 170 175

His Ile Ser Tyr Leu Phe Ser Phe His Leu Phe Lys Leu Ser Thr Phe
180 185 190

Cys Leu

<210> 181
<211> 230
<212> PRT
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<400> 181

Tyr Gly Pro Met Arg Ala Arg Leu Pro Ile Ile Cys Ser Cys Ser Pro



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1 5 10 15

Phe Pro Pro Val Gly Ser Ala Phe Ala Asn Ile His Met Tyr Phe Gln
20 25 30

Lys Asp Pro His Gly Pro His Leu Pro Ser Thr Gly Gly Arg Glu His
35 40 45

His Gly Pro Arg Thr Gly Asn Val Val Leu Val Gln Ser Tyr Gln Leu
50 55 60

Leu Pro Val Pro Phe Thr Leu Cys Arg Ser Phe Leu Gly Leu Cys Ser
65 70 75 80

Ile Phe Arg Gly His Trp Leu Lys Ser Ala Thr Met Arg His Leu Gly
85 90 95

Lys Leu Pro His Leu Val Ala Pro Leu Pro Asp Asp Thr Glu Leu Arg
100 105 110

Thr Leu Cys Ser Pro Leu Cys Tyr Phe Cys Ser Thr Gln Ser Gln Val
115 120 125

Arg Leu Ser Ser Ile Gln Arg Val Arg Gln Leu Glu Val Pro Ser Pro
130 135 140

Ile Ser Arg Met Ser Leu Ala Arg Glu Ala Ala Glu Lys Thr Tyr Leu
145 150 155 160

Gly Arg Gln Ser Lys Thr Glu Thr Lys Lys Ile Pro Ala Leu His Ala
165 170 175

Pro Ser Glu Asp His Lys Val Gly Gln Ala Gly Thr Ser Arg Trp Arg
180 185 190

Asp Ser Glu Arg His Gln Gly Leu Leu Leu Val Pro Val Ser Phe Pro
195 200 205

Pro Asn Ala Ala Ala Gln Phe Thr Val Lys Lys Val Leu Cys Phe Ser
210 215 220

His Thr Lys Gln Ala Ala
225 230

<210> 182
<211> 180
<212> PRT
<213> Homo sapiens

<400> 182

Thr Ser Pro Ser Ser Ser His Asn Lys Gln Tyr Phe Tyr Asn Thr Lys
1 5 10 15

Glu Gln Tyr Phe Ile Cys Gln Glu Lys Pro Asn Gly Leu Leu Ile Phe
20 25 30

Gly Lys Gly Lys His Ser Leu Gly Val Asn Leu Gly Ser His Leu Thr
35 40 45



BNSDOCID <WO __0162924A2_I_>

Thr Ser Tyr Arg Met Ser Ser Met Lys Val Ile Glu Leu Ile Ser Cys
    50                  55                      60

Lys Lys Lys Gly Lys Leu Asn Ala Glu Leu Lys Tyr Ser Lys Val Tyr
65                  70                  75                  80

Lys Val Gly Met Leu Val Leu Ser Thr Leu Tyr Arg Tyr Val Gln Val
                85                  90                  95

Met Phe Phe His Ile Pro Leu Thr Phe Phe Val Phe Val Tyr Ser Ala
            100                 105                 110

Met Phe Gln Asp Ala Arg Met Gln Tyr Ser Phe Arg Leu Leu Asp Asn
        115                 120                 125

Thr Ser Ser Asn Tyr Ser Val Ile Lys Ile Ile His Ser Arg Ser Ile
    130                 135                 140

Tyr Ala Leu Phe Gly Val Glu Gly Leu Asp Ile Tyr Ala Phe Ser Val
145                 150                 155                 160

Asp Asn Tyr Ile Tyr Phe Gly Tyr Ile Gly Lys Tyr Leu Thr Gln Ile
                165                 170                 175

Trp Tyr Tyr Gln
            180

<210> 183
<211> 104
<212> PRT
<213> Homo sapiens

<400> 183

Glu Tyr Glu Tyr Phe Tyr His Cys Leu Met Leu Val Arg Lys Gly Leu
1               5                   10                  15

Ala Leu Leu Ala Glu Val Gly Gly Val Cys Val His Ala Arg Thr Gly
            20                  25                  30

Thr Cys Val Leu Cys Met Cys Ile Val Cys Glu Ile Leu Gly Asn Glu
        35                  40                  45

Asn Glu Arg Ser Ser Cys Ile Leu Lys Arg Thr Ser Arg Val Leu Met
    50                  55                  60

Ser His Ser Phe Tyr Ile Leu Lys Arg Phe Ser Leu Glu Gln Tyr Leu
65                  70                  75                  80

Lys Lys Ala Tyr Ile Leu Ser Leu Ser Leu Ser His Thr His Thr Val
                85                  90                  95

Ile His Leu Tyr Thr His Ser Asn
            100

<210> 184
<211> 173
<212> PRT



BNSDOCID <WO 0162924A2 I >

<213> Homo sapiens

<400> 184

Tyr Met Phe Arg Ser Asn Pro Asn Pro Asn Lys His Ile Val Leu Gln
1 5 10 15

Cys Val Phe Ile Gln Ile Glu Tyr Ser Phe Pro Phe Leu Asn Glu Asn
20 25 30

Ser Ala Leu Glu Arg Val Ser Ser Gly Gly Asp Leu His Leu Gly Gly
35 40 45

Cys Arg Val Trp Asp Leu Phe Tyr Phe Asn Leu Tyr Arg Ala Leu Phe
50 55 60

Ile Phe Leu Phe Phe Leu Gly Glu Asn Gly Ser Leu Gln Asp Ile Leu
65 70 75 80

Lys Cys Ile Lys Phe Gly Val Asn Ser Met Trp Leu Ala Lys Ile Gln
85 90 95

Cys Leu Ser Gly Asn Lys Phe Leu Leu Tyr Ala Lys Leu Asn Asn Leu
100 105 110

Pro Gly Lys Arg Thr Ser Ser Ser Cys Leu Ser Tyr Leu Leu Pro Leu
115 120 125

Pro His Gln His Cys Leu Pro Ala Val Gln Arg Ala Leu Cys Pro Ala
130 135 140

Pro His Leu Ser Ser Cys Leu Ala Ile Leu Thr Gly Leu Leu Glu Ala
145 150 155 160

Gly Ser Gln Ser Asp Ile Ser Ser Trp Gln Phe Glu Thr
165 170

<210> 185
<211> 215
<212> PRT
<213> Homo sapiens

<400> 185

Ser Leu Val Pro Lys Gly Cys Arg Leu Leu Leu Met Met Lys Arg His
1 5 10 15

Ser Gln Val Lys Leu Ala Gln Glu Leu Tyr Ser Glu Val Pro Glu Pro
20 25 30

Ala Leu Leu Ala Ala Ser Leu Lys Leu Pro Ala Met Leu Glu Tyr His
35 40 45

Ala Asn Ser Arg Thr Thr Asp Thr His Glu Thr Lys Arg Met Asn Val
50 55 60

Thr Ser Val Pro Ile Met Asn Ala Arg Ser Glu Thr Ala Met Lys Gly
65 70 75 80



BNSDOCID <WO_ 0162924A2 I >

Lys Ser His Gly Thr Phe Phe Pro Met Thr Phe Val Ala Gly Glu Leu
85 90 95

Trp Ser Cys Gly Cys Ala Ile Lys Lys Glu Ser Ile Val Phe Phe Pro
100 105 110

Gln Ile Ile Phe Lys Phe Ser Glu Leu Pro Phe Asp Leu Thr Pro Phe
115 120 125

Ile His Ala Met Lys Ser Phe His Tyr Leu Leu Leu Val Leu Phe Gly
130 135 140

Val Ile Thr Cys Ile Asn Leu Val Ile Thr Arg Asp Thr Ser Lys Ser
145 150 155 160

Ile Trp Leu Pro Phe His Leu Leu Lys Tyr Gln Lys Thr Lys Cys Leu
165 170 175

Leu Pro Gly Thr Phe Val Lys Thr Ile Thr Lys Leu Arg Leu Leu Ser
180 185 190

Phe Phe Ile Ser Thr Ile Lys Ser Val Thr Lys Ile Arg His Tyr Ser
195 200 205

Asp Leu Leu Lys Thr Thr Leu
210 215

<210> 186
<211> 167
<212> PRT
<213> Homo sapiens

<400> 186

Asn Ile Phe Lys Pro Leu Ser Ser Gln Gly Tyr Gln Leu Lys Val Phe
1 5 10 15

Ile Gly Asn Val Tyr Tyr Met Ser Lys Phe Pro Ala Ala Leu Arg Thr
20 25 30

Ile Gly Gln Val Ile Cys Pro Leu Ile Leu Val Thr Arg Ile Arg Val
35 40 45

Leu Leu Gln Ile Trp Lys Glu Lys Leu Asp His Cys Leu Leu Tyr Tyr
50 55 60

Tyr His Pro Asn Val Tyr Arg Gly Asn Gly Pro Glu Trp Ser Lys Pro
65 70 75 80

Arg Ala Tyr Gly Glu Val Glu Leu Ser Leu Glu Val Arg Ser Ala Cys
85 90 95

Pro Lys Ala Cys Thr Leu Ala Thr Ile Leu Ser Tyr Cys Met Leu Tyr
100 105 110

Thr Thr Phe Leu Cys Leu Cys Leu Cys Ile Ser Ile Cys Leu Ser Gln
115 120 125

Glu Val Phe Phe Leu Leu Ile Ile Lys Cys Gly Phe Phe Val Val Val



BNSDOCID <WO 0162924A2 I >

130 135 140

Ile Leu Leu Lys Glu Leu Ser Cys Trp Val Gln Leu Ala Leu Thr Val
145 150 155 160

Ala Ser Leu Leu Arg Glu Pro
165

<210> 187
<211> 209
<212> PRT
<213> Homo sapiens

<400> 187

Ile Ala Ile Tyr Ile His Leu Ile Ala Asn Pro Val Gly Cys Cys Gln
1 5 10 15

Gln Leu Ala Leu Thr Ser Arg Ser Leu Thr Val Ile Gln His Ile Gln
20 25 30

Leu Asn Thr Gly Arg His Lys Ala Pro Leu Ser Pro Ala Val Lys Phe
35 40 45

Lys Met Arg Lys Ile Thr Gln Cys Leu Ser Pro Glu Cys Leu Ser Ile
50 55 60

His Lys Ser Asn Val Pro Asn Ser Ser Phe Ala Asp Cys Cys Phe Leu
65 70 75 80

Phe Arg Ser Asp Val His Gly Phe Ser Leu Gly Gln Asn Cys Glu Ile
85 90 95

Val Lys Val Thr Glu Lys Ser Leu Gln Arg Ser Ile Gly Asn Leu Leu
100 105 110

Met Thr Asn Cys Phe Cys Ile Val Pro Ile Leu Ser Asn Val Gln Val
115 120 125

Phe Thr Pro Lys Val Ser Ile Val Asn Asn Phe Tyr Phe Leu Phe Phe
130 135 140

Leu Arg Lys Cys Lys Ile Cys Phe Leu Asn Ile Glu Thr Tyr Lys Ile
145 150 155 160

Gln Lys Arg Lys Ser Ile Phe Leu Leu Pro Arg Leu Lys Ser Leu Tyr
165 170 175

Ser Tyr Phe Cys Val Tyr Arg Gly Tyr Phe Ser Ser Ile Tyr Ile His
180 185 190

Ile Lys Ser His Leu Ser Asn Gly Ile Leu Leu Phe Tyr Ile Phe Thr
195 200 205

Thr

<210> 188
<211> 233



BNSDOCID <WO__0162924A2_I_>

<212> PRT
<213> Homo sapiens

<400> 188

Leu Cys Gly Arg Ser Ala Pro Ile Ile Phe Thr Leu Phe Arg Ser Gln
1 5 10 15

Leu Tyr Ile Ile Asn Pro Trp Asp Asn Ile Gly Ile Gln Phe Lys Tyr
20 25 30

Phe Ser Ser Asp Lys Leu Asn Ala His Ile Arg Tyr Thr Phe Ala His
35 40 45

Phe Arg Ser Tyr Phe Ile Phe Trp Leu Ser Glu Arg Ala Ser Ser Lys
50 55 60

Asp Ser Phe Gln Cys Phe Leu Val Ala Tyr Ser Pro Asp Val Ser His
65 70 75 80

His Gln Leu Asn Ile Leu Arg Ala Ile Lys Arg Thr Val Phe Val Leu
85 90 95

Phe Cys Phe Leu Phe Val Pro Asn Ser Cys Leu Trp Phe Cys Gln Gly
100 105 110

Val Ile Ala Ile Phe Phe Ser His Lys Ile Ala Val Val Phe Pro Leu
115 120 125

Tyr Glu Phe Asp Cys Arg His Ala Gly Cys Leu Val Met Val Asn Phe
130 135 140

Ser Leu Leu Leu Lys Val Leu Cys Pro Ser Val Ala Val Ser Ser His
145 150 155 160

Glu Phe Ser Asp Thr Cys Phe Ile Gly Gly Glu Asn Ser Lys Pro Pro
165 170 175

Ala Arg Arg Leu Lys Asn Asn Gly Glu Asp Glu Met Thr Gln Thr Ser
180 185 190

Val His Pro Gly Lys Gln Leu Leu Ala Gly Leu Glu Cys Gly Gly Glu
195 200 205

Leu Leu Arg Glu Arg Ser Ile Ser Thr Pro Leu Ile Leu Ser Ser Cys
210 215 220

Ser Pro Ala Pro Asp Gly Gln Lys Glu
225 230

<210> 189
<211> 247
<212> PRT
<213> Homo sapiens

<400> 189

Met Met Leu Ile Asn His Leu Tyr Asn Phe Leu Gly Glu Met Ser Asn
1 5 10 15



BNSDOCID <WO 0162924A2 I >

Thr Leu Pro Ile Leu Met Gly Tyr Leu Leu Tyr Cys His Ile Val Ile
20 25 30

Leu Met Ser Gly Tyr Lys Phe Leu Ile Arg Tyr Val Val His Phe Ile
35 40 45

Ser Leu Cys Gly Phe Phe Leu Pro Asp Val Ile Ile His Thr Thr Met
50 55 60

Phe His Phe Glu Ser Ser Ile Tyr Leu Phe Phe Phe Leu Trp Leu Leu
65 70 75 80

Val Leu Leu Val Leu Asn Leu Lys Ser Gln Ser Arg Leu Thr Pro Lys
85 90 95

Ser Ser Lys Ser Val Ile Val Leu Ser Ser Tyr Ile Trp Val Gln Phe
100 105 110

Tyr Cys Phe Val Asn Leu Thr Arg Ile Ser Gln Tyr Ile Asn Ser Lys
115 120 125

Pro Met Asn Thr Cys Ser Leu Glu Lys Asn Gln Lys Ile Cys Thr Lys
130 135 140

Lys Ile Lys Gln Asn Thr Phe Ile Ile Leu Phe Ile Gln Lys Gln Leu
145 150 155 160

Leu Leu Ala Cys Trp Phe Met Leu Pro Asn Pro Ile Phe Cys Glu Cys
165 170 175

Ile Leu Ile Phe Val Tyr Ile Cys Ile Gly Met His Val Tyr Ile Leu
180 185 190

Val Gly Leu His Asn Ala His Ser Cys Val Asp Arg Phe Phe Ser Leu
195 200 205

Ile Tyr Cys Lys His Ile Cys Arg Ser Val Phe Trp Thr Trp Leu Phe
210 215 220

Thr Ser Ser Val Ser Ala Ala Glu Gln Val Leu Val Asp Asn Gln Met
225 230 235 240

Lys Cys Tyr Lys Cys Thr Leu
245

<210> 190
<211> 202
<212> PRT
<213> Homo sapiens

<400> 190

Val Val Phe Val Leu Ser Ile Phe Pro Ser Glu Ile Lys Ile Asn Thr
1 5 10 15

Cys Pro His Pro Tyr Leu Leu His Tyr Gly Pro Thr Leu Phe Ile Val
20 25 30



BNSDOCID <WO 0162924A2 I >

Gln Lys Leu Gly Leu Pro Leu Thr Phe Leu Cys Cys Tyr Ser Asn Leu
35 40 45

Leu Ser Ser Lys Phe Ile Ser Met Leu Phe Pro Leu Ser Ile Leu Gln
50 55 60

His Leu His Ile Leu Leu Phe Ala Leu Leu Asn Thr Lys Val His Ser
65 70 75 80

Asp Phe Phe Leu Ile Leu Ser Val Leu Cys Phe Leu Ala Leu Val Gly
85 90 95

Pro Phe Leu Thr Ile Asn Ile Phe Ser Ile Ser Ser His Tyr Leu His
100 105 110

Leu Leu Asn Leu Thr Leu Tyr Ser Thr Ala Ile Tyr Phe Leu Glu Leu
115 120 125

Leu Ile Ser Arg Thr Phe Leu Ile Leu Tyr Ile Leu Asn Thr Val Tyr
130 135 140

Phe Ser Arg Ala Trp Lys Lys Lys Val Ser Leu Ile Gln Val Val Asn
145 150 155 160

Ile Gln Ser Pro Asn Lys Cys Leu Leu Ser Thr Asp Tyr Ile Pro Ser
165 170 175

Thr Pro Val Gly Ser Arg His Val Arg Asn Glu Ala Ile Lys Ile Ser
180 185 190

Thr Leu Thr Glu Ile Lys Phe Ser Gly Glu
195 200

<210> 191
<211> 205
<212> PRT
<213> Homo sapiens

<400> 191

Leu Cys Leu Lys Ile Ile Ile Ile Lys Asn Ile Tyr Leu Tyr Met Val
1 5 10 15

Tyr Glu Phe Asp Thr Phe Cys Phe Ile Ser Gly Leu Met Cys Tyr Arg
20 25 30

Lys Gly Met Thr Leu Asn Ser Leu Asn Phe Ser Leu Ile Ala Leu Asp
35 40 45

His Phe Gln Leu Ser His Leu Tyr Asn Ile Gly Gln Val Thr Pro His
50 55 60

Ala Tyr Phe Ala Ile Tyr Lys Ser Ala Asn Arg Thr Leu Ile Gly Leu
65 70 75 80

Leu Arg Gly Ile Ser Lys Thr Ile Glu Ser Ser Ile Trp Trp Gly Ser
85 90 95

Thr Asn Ile Ser Thr Leu Leu Thr Leu Phe Phe Ser Pro Cys Tyr Ala



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            100                 105                 110

Phe Gln Phe Ile Ser Thr Lys Leu Val Ile Lys Ile Gln Ala Glu Val
        115                 120                 125

Leu Leu Ile Ser Leu Cys Val Leu Pro Gly Ser Tyr His Ser Ala Arg
    130                 135                 140

Asp Thr Gln Ala Pro Ser Phe Met Val Asn Thr Asp Ser Glu Leu Cys
145                 150                 155                 160

Leu Arg Pro Phe Gly Met Leu Gln Gln Asn Thr Ile Asp Arg Val Thr
                165                 170                 175

Tyr Lys Pro Gln Lys Cys Val Ser Tyr Arg Ser Gly Gly Trp Glu Val
            180                 185                 190

Gln Asp His Gly Ile Val Arg Phe Ser Val Trp Arg Pro
        195                 200                 205

<210>  192
<211>  197
<212>  PRT
<213>  Homo sapiens

<400>  192

Ala His Cys Val Phe Ile Ile Met Glu Glu Gln Trp Ser Leu Lys Leu
1               5                   10                  15

Gln Ile Ile Pro Ser Pro His Cys Gly His Leu Phe Leu Ser Asn Leu
            20                  25                  30

Ser Leu Glu Gln Leu Ala Arg Met Gln Asn Leu Met Ile Phe Ser Leu
        35                  40                  45

Pro Leu Leu Asp Pro Ala Tyr Thr Pro Pro Leu Val Glu Val Pro Arg
    50                  55                  60

Ser Ser Glu Met Thr Lys Arg Gln Gly Val Gly Gly Arg Gly Lys Lys
65                  70                  75                  80

Asn Lys Pro Ser Asp Gln Pro Gln Met Thr Glu Cys Trp Leu Phe Ser
                85                  90                  95

Ile Ile Tyr Ser Phe Glu Leu Ser Gln Met Cys Phe Ser Glu Lys Thr
            100                 105                 110

Phe Met Leu Ser Phe Leu Ser Ser Leu Ile Val Asn His Gln Phe Pro
        115                 120                 125

Cys Asn Gly Leu Arg Val Gln Ser Pro Met Arg Ser Arg Ala Ala Arg
    130                 135                 140

Phe Ser Arg His Ser Thr Thr Phe Pro Ser Pro Phe Phe Lys Gln Ala
145                 150                 155                 160

Phe Lys Leu Cys Met Lys Pro Cys Gln Thr Lys Met Lys Val Thr Lys
                165                 170                 175
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Val Lys Ile Gln Lys Gln Phe Ile His Pro Arg Tyr Leu His Thr Ala
            180                 185                 190

Leu Asn Met Val Asp
        195

<210>  193
<211>  207
<212>  PRT
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<400>  193

Pro Ser Ser Trp Lys Leu Leu Phe Tyr Thr Leu Ile His Ser Gly Ile
1               5                   10                  15

His Tyr Gln Val His Arg Val Val Lys Phe Arg Ile Arg Glu Asn Val
            20                  25                  30

Glu Lys Val Ser Ala Arg Leu Leu Pro Lys Tyr Trp Ser Asn Ile His
        35                  40                  45

Gln Thr His Met Val His Glu Gly Gln Thr Ser Ile Ile Cys Ser Cys
    50                  55                  60

Ser Pro Phe Pro Pro Val Gly Ser Ala Phe Ala Asn Ile His Met Tyr
65                  70                  75                  80

Phe Gln Lys Asp Pro His Gly Pro His Leu Pro Ser Thr Gly Gly Arg
                85                  90                  95

Glu His His Gly Pro Arg Thr Gly Asn Val Val Leu Val Gln Ser Tyr
            100                 105                 110

Gln Leu Leu Pro Val Pro Phe Thr Leu Cys Arg Ser Phe Leu Gly Leu
        115                 120                 125

Cys Ser Ile Phe Arg Gly His Trp Leu Lys Ser Ala Thr Met Arg His
    130                 135                 140

Leu Gly Lys Leu Pro His Leu Val Ala Pro Leu Pro Asp Asp Thr Asp
145                 150                 155                 160

Leu Arg Thr Leu Cys Ser Pro Leu Cys Tyr Phe Cys Ser Thr Gln Ser
                165                 170                 175

Gln Val Arg Leu Ser Ser Ile Gln Arg Val Arg Gln Leu Glu Val Pro
            180                 185                 190

Ser Pro Ile Ser Arg Met Ser Leu Ala Arg Glu Ala Ala Glu Lys
        195                 200                 205

<210>  194
<211>  179
<212>  PRT
<213>  Homo sapiens

<400>  194
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BNSDOCID <WO 0162924A2 I >

Ile Gln Gln Lys Arg Arg Arg His Arg Ala Thr Arg Lys Ile Gly Ile
1 5 10 15

Ala Ile Ala Thr Phe Leu Ile Cys Phe Ala Pro Tyr Val Met Thr Arg
20 25 30

Trp Val Leu Ala Val Arg Leu Leu Leu Trp Glu Gln Leu Gly Gly Leu
35 40 45

Gly Leu Ser Val Gly Leu Gly Phe Pro Ala Arg Tyr Leu Glu Gly Gly
50 55 60

His His Gln Arg Thr Leu Leu His Thr Arg Ala Gln Gly Cys Ala Ser
65 70 75 80

Ala Pro Gly Lys Asp Pro Gly Arg Glu Val Ala Leu Ala Pro Ile Leu
85 90 95

Ser Tyr Lys Gly Asp Ser Pro Cys Pro Gly Thr Gly Arg Tyr Gly Val
100 105 110

Cys Glu Ser Ala Pro Gly Ser Leu Asn Leu Glu Ser Phe Gln Asn Gln
115 120 125

Ala Thr Trp Asp Leu Arg Pro Gln Thr Pro His Leu Leu Gly Val Glu
130 135 140

Leu Gly Ile Trp Val Glu Ala Pro Ala Gly Ala Ser Gly Gln His Cys
145 150 155 160

Gln Val Ser Val Leu Phe Ala Ser Leu Phe Pro Gly Asp Leu Gly Leu
165 170 175

Ser Ala Cys

<210> 195
<211> 138
<212> PRT
<213> Homo sapiens

<400> 195

Arg Asn Ser Val Glu Arg Ala Ser Val Leu Asn Val Val Lys Val Tyr
1 5 10 15

Thr Glu His Gly Pro Phe Ile Trp Val Arg Glu Thr Thr Ser Pro Phe
20 25 30

Val Leu Ser His Phe Leu Leu Val Phe Leu Thr His Ile Ala Asp Val
35 40 45

Ile Leu Met His Lys Tyr Leu Gly Lys Val Ser Glu Ala Gly Phe Leu
50 55 60

Leu Val Phe Pro His Ser Leu Ser Val Val Cys Phe Tyr Ile Leu Cys
65 70 75 80



BNSDOCID <WO__ 62924A2_I >

Asp Phe Pro Ile Thr Phe Leu Cys Phe Tyr Arg Arg Ser Arg Ser Cys
85 90 95

Leu Thr His Leu Trp Thr Leu Ala Asn Gly Met Arg Gly His Met Pro
100 105 110

Phe Leu His Pro Ser Arg Ser Leu Met Trp Leu Gln Arg Ala Gln Gly
115 120 125

Leu Tyr Ser Gly Ser Leu Pro Ala Gln His
130 135

<210> 196
<211> 196
<212> PRT
<213> Homo sapiens

<400> 196

Phe Thr Lys Pro Ile Ile Ile Ser Asn Pro Asn Arg Asp Leu Trp Leu
1 5 10 15

Leu Ser Ile Lys Gly Asn Lys Ala Pro Ser Pro Ile Leu Ile Ile Phe
20 25 30

Ser Phe Leu Phe Tyr Phe Leu Ser Phe Phe Asn Met Phe Gln Cys Gln
35 40 45

Asn Arg Leu Ala His Leu Cys Ser Pro Ala Ala Phe Pro Arg Arg Ala
50 55 60

Ala Ser Asn Ser Leu Trp Ser Gln Trp Ala Ile Ile Arg Gly Asn Thr
65 70 75 80

Cys Met Leu Lys Ser Ile Cys Pro Leu Thr Ile Asp Lys Gln Ala Leu
85 90 95

Asn Lys Lys Ser Ser Thr Gln Ile Ser Phe Leu Asn Ala Val Leu Phe
100 105 110

Leu Arg Phe Lys Asn Ser Ser Thr Pro Phe Ile Leu His Ile Tyr Phe
115 120 125

Thr Thr Ala Leu Leu Thr Ser Phe Pro Ile Leu Ala Gln Asn Phe Tyr
130 135 140

Glu Glu Asn Leu Arg Ile Thr Ala Leu Val Thr Cys Trp Ser Gly His
145 150 155 160

His Ala Phe Phe Ile Trp Gln Leu Ile Gln Ser Leu Phe His Asn Lys
165 170 175

Ser Asp Leu Glu Ser Gln Arg Lys Lys Lys Leu Arg Thr Cys Trp Glu
180 185 190

Ser Pro Val Ser
195

<210> 197



BNSDOCID <WO 0162924A2 I >

<211> 116
<212> PRT
<213> Homo sapiens

<400> 197

Phe Val Phe Lys Leu Val Thr His Thr His Thr Ser Ser Ala Arg His
1 5 10 15

Thr Met Lys Thr Val Ala Pro Val His Phe Ser Leu Leu Val Pro Arg
20 25 30

Gly Asn Tyr Phe Leu Leu Ile Val Phe Phe Trp Tyr Leu Ser Pro Tyr
35 40 45

Leu Ser Leu Tyr Cys His Phe Leu Ile Phe Gln Phe Ser Thr Leu Ile
50 55 60

Phe Gln Phe Phe His Ala Gly Arg Arg Gly Phe Asn Tyr Phe Leu Leu
65 70 75 80

Ser Phe Pro Val Thr Gln Tyr His Thr His Thr Pro Ser Leu Thr Pro
85 90 95

Thr Leu Ser Ile Phe Ser Leu Lys Ser Ile Ile Asn Ile Tyr Ile Ile
100 105 110

Ile Met Cys Arg
115

<210> 198
<211> 220
<212> PRT
<213> Homo sapiens

<400> 198

Ala Pro Val Lys Ile Ser Val Leu Gln Asp Lys Arg Cys Gly Gln Gly
1 5 10 15

Thr Gln Ser Leu Ile Glu Val Leu Met Leu Pro His Ser Trp Ala Asp
20 25 30

Ala Ile Leu Leu Trp Glu Leu Thr Ser Ser Pro Cys Thr Thr Ser Glu
35 40 45

Gly Ser Ser Pro Ser Ile Leu Tyr Cys Thr Tyr Leu Thr His Thr Leu
50 55 60

His Ser Ser Ala His Phe Leu Arg Val Arg Ala Phe Ser Ile His Ser
65 70 75 80

Ile Leu Trp Phe Leu Asn Leu Trp His Gly Phe Leu Ile Arg Asp Pro
85 90 95

Gln Glu Ile Thr Arg Lys Thr Asp Thr Gln Ala Pro Ser Cys Asn Pro
100 105 110

Arg Gln Asp Glu Leu Ser Thr Lys Ile Glu Lys Pro Leu Arg Val Pro



BNSDOCID <WO 0162924A2_I >

115 120 125

Trp Arg Ala Val Gly Lys Ser Gly Val Arg Ser Ser Thr Ser Gln Gly
130 135 140

His Thr Leu Pro Leu Ser Pro Leu Ser Cys Met Ser Ser Gly Lys Leu
145 150 155 160

Ser Lys Leu His Gly Gln Gly Cys Leu Asp Asp Thr Cys Gly Gln Gln
165 170 175

His Pro His Ile Pro Arg Asp Val Glu Lys Pro Lys Lys Gly Ala Ala
180 185 190

Trp Arg Glu Phe Trp Gly Lys Glu Arg Gln Phe Cys Val Asp Cys Gln
195 200 205

Asp Gln Pro Cys Leu Leu Arg Cys Leu Glu Gln Ala
210 215 220

<210> 199
<211> 200
<212> PRT
<213> Homo sapiens

<400> 199

Leu Leu Phe Leu Val Tyr Thr Ile Ser Thr Thr Gly Val Val Gly Asp
1 5 10 15

Lys Asp Asn Ile Phe Ser Pro Leu Ser Thr Pro Phe Leu Phe Cys Pro
20 25 30

Phe Cys Gly Pro Ile Ile Cys Gln His Leu Lys Ile Gly Ser His Leu
35 40 45

Leu Arg Ile Lys Met His Pro Tyr Pro Gly Ser Phe Ser Met Ser Arg
50 55 60

Ile Thr Ile Ser Lys His Ala Tyr Pro Asn Leu Thr Cys Gln Leu Gln
65 70 75 80

Trp Thr Leu Ile Ser Thr Ser Leu Pro Pro Ala Pro Ser Ser Val Leu
85 90 95

Cys Ile Ile Gln Lys Tyr Ser Ser Ser Glu Val Arg Leu Trp Tyr Thr
100 105 110

Ile Phe Leu Ile Ile Ile Trp Phe Ser Tyr Phe Ile Thr His Ile Ser
115 120 125

Phe Ile Leu Asn Leu Ser Leu Phe Cys Asn Leu Ser Leu Pro Ser Leu
130 135 140

Phe Ile Ser Val Met Val Trp Val Phe Leu Ser Leu Gln Asn Ser Cys
145 150 155 160

Asn Val Ser Ser Ala Ser Val Leu Lys Arg Trp Gly Leu Gly Gly Asp
165 170 175



BNSDOCID <WO 0162924A2 I >

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Val Thr Lys Val Pro Pro Ser Met Gly Leu Arg Thr Leu Tyr Lys Arg
            180                 185                 190

Leu His Thr Ala Phe Ser Cys Phe
        195                 200

<210>  200
<211>  198
<212>  PRT
<213>  Homo sapiens

<400>  200

Ser Ala Ile Val Ile Phe Leu Ser Ser Phe Leu Cys His Phe Leu Phe
1               5                   10                  15

Ile Phe Gly Arg Arg Met Leu Ser Tyr Tyr Lys Pro Tyr Lys Cys Lys
            20                  25                  30

Leu Ile Ile Val Arg Lys Cys Tyr Ile Ser Glu Cys Leu Leu Arg Leu
        35                  40                  45

Ser Thr Phe Trp Cys Pro Tyr Ala Ala Pro Cys Cys Pro Val Ser Thr
    50                  55                  60

Leu Thr Glu Asn Cys Pro Lys Leu Pro Thr Phe Ser Thr Ser Leu Tyr
65                  70                  75                  80

Ser Ala Ile Lys Thr Tyr Leu Ala Arg Asp Pro Asp Cys Trp Ser Phe
                85                  90                  95

Pro Pro Gln Cys Gln Trp Val Asn Arg Gln Ile Lys Glu Arg Ser Ser
            100                 105                 110

Ser Leu Phe Ile Tyr Pro Phe Ile Ile Phe Trp Gln Leu Thr Gln Ala
        115                 120                 125

Phe Glu Leu Val Leu Cys Gly Gln Cys Leu Ile Ser Arg Phe Pro Ser
    130                 135                 140

Leu Gly Phe Gln Thr Leu Pro Val Leu Val Gln Ala Thr Leu Met Asp
145                 150                 155                 160

Leu Ser Leu Pro Val Ser Asn Leu Cys Thr Ser Pro Thr Leu Tyr Pro
                165                 170                 175

His Trp Leu Leu Ala Val Phe Pro Thr Ala Thr Cys Val Leu Pro Ser
            180                 185                 190

Leu Pro Val Pro Thr Leu
        195

<210>  201
<211>  206
<212>  PRT
<213>  Homo sapiens

<400>  201
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BNSDOCID <WO ._ 0162924A2 I >

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Ser Thr Arg Cys His Arg Cys Ser Val Pro Trp Pro Gly Pro Phe Trp
1               5                   10                  15

Arg His Gln Thr His Asp Lys Ala Gln Ala Val Arg Lys Glu Lys Asn
            20                  25                  30

Leu Val Leu Ser Ser Phe Leu Gln Ser Glu Arg Trp Met Cys Val Thr
        35                  40                  45

Leu Ser Leu Leu Glu Thr Leu Ile Lys Trp Phe Leu Leu Met Val Leu
    50                  55                  60

Leu Ser Leu Arg Thr Leu Arg Ala Gly Val Gly Met Asn Leu Cys Asp
65                  70                  75                  80

Ile Tyr Ala Tyr Ser Glu Ser Leu Leu Ser Ser Lys Asn Val Val Lys
                85                  90                  95

Leu Glu Pro Val Phe Phe Leu Ser Ser Gln Glu Asp Leu Arg Lys Ser
            100                 105                 110

Gln Ser Cys Thr Lys Phe Ser Cys Phe Ile Asn Arg Ser Pro Ala Ile
        115                 120                 125

Ser Thr Phe Trp Leu Lys Leu Tyr Ile Phe Thr Tyr His Asn Asp Cys
    130                 135                 140

Leu Val Asn Asp Phe Leu Ser Tyr Gln Leu Leu Glu Ser Tyr Thr Thr
145                 150                 155                 160

Phe Arg Ala Thr Val Ser Phe Leu Leu Phe Leu Tyr Trp Ile Leu Val
                165                 170                 175

Gln Phe Ser His Pro Lys Thr Leu Met Ala Tyr Asn Ile Ile Pro Met
            180                 185                 190

His Ile Leu Ser Tyr Thr Ser Asn His Leu Ile Ile Tyr Asn
        195                 200                 205

<210>  202
<211>  167
<212>  PRT
<213>  Homo sapiens

<400>  202

Thr Ser His Thr His Gly Ser Ser Ser Met Ile His Thr Leu Thr Gly
1               5                   10                  15

Ile Asn Leu Pro Leu His Phe Trp Pro Arg Arg Thr Phe Ser Asp Trp
            20                  25                  30

Gly Ser Lys Glu Ile Thr Glu Ile Ile Lys Arg Lys Ile Ile Ser Gln
        35                  40                  45

Asp Ser Phe Ala Thr Tyr Leu Ala Leu Lys Leu Arg Phe Ser Glu His
    50                  55                  60
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BNSDOCID <WO__0162924A2_I_>

Cys Ile Leu Pro Gln Thr Thr His Thr His Thr His Ile Glu Tyr Phe
65 70 75 80

Lys Ile Arg Asn Trp Ala Thr Tyr Asn Ser Gly Lys Arg His Leu Asn
85 90 95

Gly Thr Glu His His Ile Tyr Glu Ser Ser Val Gln Arg Ile Ser Glu
100 105 110

Asn Val His Lys Val Ser Ala Phe His Arg Leu Gly Ile Glu Ala Val
115 120 125

Ala Ile Thr Ile Lys Ile Gln Ala Gln Gly Lys Met Lys Leu Gly Val
130 135 140

Lys Gly Ser Glu Ile His Phe Arg Lys Ala Phe Lys Ala Arg Lys Met
145 150 155 160

Arg Ser Thr Trp Tyr Val Phe
165

<210> 203
<211> 181
<212> PRT
<213> Homo sapiens

<400> 203

Asn Lys Ser Ser Lys Gly Asn Ile Phe Arg Cys Phe Tyr Tyr Phe Leu
1 5 10 15

Phe Phe Ile Phe Leu Leu Trp Lys Leu Leu Val Gln Thr Ala Pro Phe
20 25 30

Cys Asn Pro Pro Ala Ile Ser Gln Thr Ser Val Lys Val Lys His Ser
35 40 45

Thr Gly Val Arg Ala Val Thr Asn Ser Leu Pro Asn Arg Leu Thr Leu
50 55 60

Leu Leu Tyr Ser Ala Gly Arg Lys Cys Lys Glu Pro His Thr Ala Leu
65 70 75 80

Glu Gln Ala Pro Asn Cys Leu Ile Met Gly Thr Cys Tyr Gln His Phe
85 90 95

Pro Arg Gln Gln Ala Met Pro Pro Val Pro Asp Pro Ser His Leu Ala
100 105 110

Tyr Asn Cys Pro Ser Leu Val Ala Met Ala Ile Gly Ile Lys Leu Gln
115 120 125

Val Leu Cys Trp Thr Ser Arg His Leu Leu Ser His His Ser Leu Ser
130 135 140

Leu Cys Leu Ser Leu Thr Leu Ala Phe Pro Ser Lys Pro Asn Lys Asn
145 150 155 160

Tyr Leu Asp Asn Phe Ser Ser Ser Ser Ser Lys Asn Leu Ile Phe Cys



BNSDOCID <WO 0162924A2 I >

165 170 175

Leu Phe Val Leu Val
180

<210> 204
<211> 186
<212> PRT
<213> Homo sapiens

<400> 204

Ala Arg Leu Arg His Gln Ser Asn Gly Leu Val Leu Ser Ser Pro Gly
1 5 10 15

Gly Leu Ile Lys Gly Gly Ser Leu Gly Asn Val Ser Val Ile Gly Pro
20 25 30

Ser Val Asn Thr Tyr Leu Ala Asn Ala Ser Ser Lys Trp Pro Gly Ala
35 40 45

Ala Phe Arg Thr Leu Arg Arg Phe His Asn Val Val Leu Arg Met Val
50 55 60

Phe Leu His Trp Ile Phe Phe Leu Pro Phe Gln Leu Tyr Lys Leu Phe
65 70 75 80

Tyr Glu Lys Gly Gly Asn Ala Lys Gly Ile Gly Val Gly Gly Asn Val
85 90 95

Lys Ile Leu Gln Asp Pro Ala Ser Ile Phe Gly Ala Gln Arg Glu Pro
100 105 110

Gly Ser Thr Phe Leu Asn Thr Gly Gly Thr Gly Gly Met Glu Ala Trp
115 120 125

Ser Gly Gly Ala Cys Gly Gln Thr Pro Ala Ala Leu Ser Thr Tyr His
130 135 140

Ile Met Ala Trp Gln Thr Ser Ser Pro Ser Lys His Arg Leu Leu Ala
145 150 155 160

Asp Ser Pro Gln Lys Asp Met Pro Gly Val Asp Ala Trp Asn Ser Leu
165 170 175

Leu Ile Tyr Trp Asn Pro Lys Ile Lys Gln
180 185

<210> 205
<211> 249
<212> PRT
<213> Homo sapiens

<400> 205

Phe Lys Ile Val Ser Leu Phe Leu Tyr Lys Pro Ser Arg Leu Gln Lys
1 5 10 15

Phe Lys Asn Thr His Glu Val Gly Asn Cys Ile His Phe Leu Ser Thr



BNSDOCID <WO__0162924A2_I_>

20 25 30

Gln His Ser Met Thr Asp Leu Val Val Leu Asn Asn Thr Asn Leu Leu
35 40 45

Ser Gln Ser Ser Leu Asp Gln Lys Phe Asn Ile Gly Ser Ala Lys Ile
50 55 60

Lys Gly Leu Ala Cys Ala Ser Tyr Arg Phe Gly Arg Ile His Phe Gln
65 70 75 80

Val His Ala Tyr Cys Trp Leu Asn Ser Ile Pro Cys Ser Tyr Arg Ile
85 90 95

Ile Pro Val Phe Leu Leu Ala Lys Gly Leu Asn His Phe Leu Pro Leu
100 105 110

Glu Ile Val Cys Phe Pro Tyr Leu Met Ala Leu Leu Ser Ser Lys Ser
115 120 125

Ala Ile Met Ile Gln Val Leu Pro Phe Ile Ser Ser Val Ile Tyr Ser
130 135 140

Asp Met Ser Ser Leu Pro Ser Leu His Leu Thr Leu Leu Pro Ser Ser
145 150 155 160

Ile Cys Lys Gly Pro His Thr Asn Pro Glu Ser Leu Tyr Phe Lys Ile
165 170 175

Asn Leu Leu Glu Pro Phe His Leu Gln Asn Cys Val Ser Ile Tyr His
180 185 190

Asn Ile Ser Thr Gly Ile Trp His Lys Arg Val Thr Ile Met Ala Cys
195 200 205

Val Ser His Lys Ile Thr Ala Pro Asn Arg Ile Thr Ser Lys Leu Ala
210 215 220

Tyr Phe Tyr Ile Asn Pro Pro Lys Asp Asn Cys Arg Ser Ser Ser Lys
225 230 235 240

Ile Pro Asp Met Lys Leu Ala Ile Ala
245

<210> 206
<211> 240
<212> PRT
<213> Homo sapiens

<400> 206

His His Ser His Leu His Gln Pro Thr Arg Ala Pro Val Gly Glu Gly
1 5 10 15

Lys Leu Ser Lys Cys Leu Trp Gly Ser Ser Val Gly Ser Leu Arg Arg
20 25 30

Gln Gly Leu Leu Gly Arg Ala Phe Arg His Gly Arg Gly Arg Arg Glu
35 40 45



BNSDOCID <WO 0162924A2 I >

Gly Thr Gln Asn Gln Glu Gly Val Gly Gly Ser Asp Leu Met Ser Gln
    50                  55                  60

Lys Thr Phe Trp Lys Ser Gly Leu Pro Ala Leu Glu Gly Met Thr Leu
65                  70                  75                  80

Ser Arg Val Pro Cys Lys Asp Ser Pro Glu Arg Leu Pro Asn Ser Ser
                85                  90                  95

Arg Asp Pro Gly Ala Asp Cys His Pro Thr Arg Val Arg Pro Gly Arg
            100                 105                 110

Cys Val Leu Pro Arg Ala Leu Gln Thr Phe Gly Ala Cys Lys Gly Asn
        115                 120                 125

Gly Glu Ser Leu Trp Gln Arg Gln Arg Leu Gln Ser Glu Cys Lys Met
    130                 135                 140

Ala Lys Ile Met Leu Leu Val Ile Leu Leu Phe Val Leu Ser Trp Ala
145                 150                 155                 160

Pro Tyr Ser Ala Val Ala Leu Val Ala Phe Ala Gly Ala Val Ala Lys
                165                 170                 175

Gly Leu Gly Lys Arg Leu Lys Val Trp Gly Gln Glu Gln Glu Ala Trp
            180                 185                 190

Pro Ala Ser Pro Ser Gln Pro Asn Pro Gly Gln Pro Ser Ser His Pro
        195                 200                 205

Arg Thr Ser Phe Thr Ala Tyr Ser Leu Pro Trp Val Arg Cys Pro Ala
    210                 215                 220

Pro Gly Trp Val Gly Gly His Leu Val Pro Gly Ser Thr Arg Ala His
225                 230                 235                 240

<210> 207
<211> 170
<212> PRT
<213> Homo sapiens

<400> 207

His Arg Ile Phe Lys Ala Phe Ser Gln Val Thr Phe Asp Cys Ile Asn
1               5                   10                  15

Ser Ile Phe Phe Leu Leu Leu Ile Leu Cys Phe Cys His Asn Leu Leu
            20                  25                  30

Leu Leu Tyr Cys Ile Cys Leu Asn Lys Leu Leu Asn Leu Leu Leu Phe
        35                  40                  45

Leu Ile Val Leu Phe Phe Asn Leu His Thr Lys Asp Ile Ser Asn His
    50                  55                  60

Ile Thr Ile Thr Ile Leu Lys Cys Ser Glu Phe Asp Tyr Ala Phe Thr
65                  70                  75                  80



BNSDOCID <WO 0162924A2 I >

Phe Ala Tyr Lys Cys Ile Cys Leu Asn Lys Leu Leu Asn Leu Leu Leu
85 90 95

Phe Leu Ile Val Leu Phe Phe Asn Leu Tyr Thr Leu Tyr Val Tyr Val
100 105 110

Leu Val Ile Ser Ile Leu Phe Phe Gln Val Phe Ser Asn Ile Lys Asn
115 120 125

Ser Ile Ser Ile Ser Cys Lys Thr Gly Met Val Leu Leu Asn Ser Leu
130 135 140

Ser Phe Phe Leu Gly Lys Pro Leu Ser Leu Phe Leu Phe Leu Lys Asp
145 150 155 160

Ser Phe Ala Met Tyr Ser Ile Leu Phe Trp
165 170

<210> 208
<211> 174
<212> PRT
<213> Homo sapiens

<400> 208

Thr Val Ser Val Thr Gln Tyr Ile His Ala Trp Ile Phe Ile Pro Val
1 5 10 15

Phe Leu Phe Ser Ile Cys Tyr Thr Leu His Ile Leu Gly His Cys Ser
20 25 30

Ser Arg Pro Asn Asp Arg Gly Gln Met Asn His Tyr Val Leu Leu Ser
35 40 45

Met Leu Lys Gly Lys Lys Ser Ile Asn Ser Met Phe Ile Tyr Cys Phe
50 55 60

Tyr Leu Pro Met Ile Phe Phe Ile Leu Gly Gln Lys Phe Asn Leu Ser
65 70 75 80

Tyr Ile Phe Gln Thr Phe Lys Met Phe Ala Val Ile Phe Ser Thr Ser
85 90 95

Trp Gln Gln Ile Cys Phe Arg Ile Cys Ser Leu Tyr Tyr Ser Cys Leu
100 105 110

Cys Val Cys His Thr Glu Ser Thr Phe Gln Lys Leu Leu Lys Glu Ile
115 120 125

Thr Glu Met Lys Val Met Asn Ala Ile Leu Leu Glu Ile Asn Phe Leu
130 135 140

Ser Lys Asp Asn Arg Gly Ser Val Leu Ser Glu Glu Pro Gly Ala Ile
145 150 155 160

Leu Lys Ser Leu Ile Ser Leu Pro Pro Phe His Gly Met Tyr
165 170

<210> 209



BNSDOCID <WO __0162924A2 | >

<211> 165
<212> PRT
<213> Homo sapiens

<400> 209

Gly Pro Arg Asp Leu Ser Thr Ser Leu Gly His Met Gly Trp Leu Arg
1               5                   10                  15

Ala Leu Gln Arg Glu Thr Leu Pro Gln Trp Gly Pro Arg Pro Val Lys
            20                  25                  30

Arg Glu Ile Lys Thr Lys Ser Ala Asp Phe Gln Ser Ser Ser Phe Asn
        35                  40                  45

Ile Ser Lys Ser His Lys Asn Tyr Ser Arg Glu Leu Val Glu Arg Leu
    50                  55                  60

Glu Leu Gly Arg Lys Ala Gly Tyr Ile Phe Leu Phe Ser Asn Phe Ser
65                  70                  75                  80

Ser Tyr Thr Trp His Leu Ser Ser Leu Leu Leu Leu Leu Phe Arg Leu
                85                  90                  95

Leu Trp Pro Gln Glu Gly Gly Met Leu Asp Gly Trp Arg Ala Arg Glu
            100                 105                 110

Gly Leu Arg Cys Asn Ser Tyr Phe His Val Cys Asp Asn Ala Val Ala
        115                 120                 125

Met Leu Phe Ser Glu Ala Ser Ser Cys Thr Gln Gly Val Leu Leu Met
    130                 135                 140

Gln Arg Gly Arg Phe Gln Cys Leu Ala Val Val Tyr Leu Pro Cys Arg
145                 150                 155                 160

Cys Ser Gly Gln Gln
                165

<210> 210
<211> 167
<212> PRT
<213> Homo sapiens

<400> 210

Thr Ser His Thr His Gly Ser Ser Ser Met Ile His Thr Leu Thr Gly
1               5                   10                  15

Ile Asn Leu Pro Leu His Phe Trp Pro Arg Arg Thr Phe Ser Asp Trp
            20                  25                  30

Gly Ser Lys Glu Ile Thr Glu Ile Ile Lys Arg Lys Ile Ile Ser Gln
        35                  40                  45

Asp Ser Phe Ala Thr Tyr Leu Ala Leu Lys Leu Arg Phe Ser Glu His
    50                  55                  60

Cys Ile Leu Pro Gln Thr Thr His Thr His Thr His Ile Glu Tyr Phe



BNSDOCID <WO_0162924A2_I_>

65 70 75 80

Lys Ile Arg Asn Trp Ala Thr Tyr Asn Ser Gly Lys Arg His Leu Asn
85 90 95

Gly Thr Glu His His Ile Tyr Glu Ser Ser Val Gln Arg Ile Ser Glu
100 105 110

Asn Val His Lys Val Ser Ala Phe His Arg Leu Gly Ile Glu Ala Val
115 120 125

Ala Ile Thr Ile Lys Ile Gln Ala Gln Gly Lys Met Lys Leu Gly Val
130 135 140

Lys Gly Ser Glu Ile His Phe Arg Lys Ala Phe Lys Ala Arg Lys Met
145 150 155 160

Arg Ser Thr Trp Tyr Val Phe
165

<210> 211
<211> 202
<212> PRT
<213> Homo sapiens

<400> 211

Ser Thr Gly Phe Phe Ser Met Pro Leu Phe His Phe Gln Pro Ile Ser
1 5 10 15

Ser Ile His Cys Leu Ala Ser Tyr Pro Asn Cys Thr Lys Pro Ala Gln
20 25 30

Ser Leu Trp Glu Asp Phe Glu Asn Ala Phe Ser Cys Val Ala Ser Leu
35 40 45

Val Ser Ile Lys Leu Ser Thr Thr Met Pro Trp Cys Gln Cys Ile Leu
50 55 60

Ser Val Gln Cys Ala Glu Arg Thr His Trp Gln Leu His Tyr Gln Leu
65 70 75 80

Ser Leu Phe Cys Pro Ser Asn Arg Lys Tyr Phe Asn Pro Gly Lys Ser
85 90 95

Ile Arg Val Ser His Ser Phe Ala Glu Leu Leu Val Ala Trp Pro Glu
100 105 110

Thr Leu Ser Ala Ala Pro Val Thr Gln Trp Pro Phe Ser Phe Ser Glu
115 120 125

Thr Phe Phe Leu Asn Leu Cys Val Pro Cys Leu Asn Leu Tyr Trp Leu
130 135 140

Ile Ser Arg Pro Val Lys Leu Ser Ile Leu Thr Pro Ser Leu Pro Ser
145 150 155 160

Arg Asn Ala Ile Cys Leu Ser Phe Leu Ser Tyr Leu Leu Leu Pro Gly
165 170 175



BNSDOCID <WO 0162924A2 I >

Phe Trp Glu Val Tyr Ala Leu Gly Asp Lys Tyr Pro Ser Glu Lys Lys
180 185 190

Asn Thr Asn Phe Phe Lys Phe Phe Thr Pro
195 200

<210> 212
<211> 155
<212> PRT
<213> Homo sapiens

<400> 212

Met His Leu Pro Tyr Leu Leu Leu Ser Phe Pro Tyr Pro Gln Asn Ile
1 5 10 15

Val Ser Leu Trp Ile Ala His Ser Trp Pro Asp Lys Gln Leu Ser Asn
20 25 30

Thr Ile Tyr Asn Leu Ser Val Asn Ile Phe Leu Ser Pro Pro Leu Leu
35 40 45

His Cys Lys Phe Ser Ser Met Gly Ser Cys Leu Val Tyr Ser Arg His
50 55 60

Ser Gly Thr Asn His Asn Leu Trp Ser Glu Asn Cys Ile Leu Tyr His
65 70 75 80

Gly Ser Thr Thr Lys Val Thr Leu Arg Thr Cys Pro Asp Gly Asn Phe
85 90 95

Phe His Phe Gln Asn Val Ser Asp Pro Leu Ser Phe Gln Cys Leu Gln
100 105 110

Val Ile Trp Val Tyr Thr Phe Glu Asn Lys Asn Phe Leu Gly Ile Ser
115 120 125

Ile Leu Ile Phe Asn Ile Gln Ile Lys Cys Val Met Cys Phe Ile Leu
130 135 140

Leu Lys Ser Phe Pro Ile Ser Tyr Phe Asn Lys
145 150 155

<210> 213
<211> 190
<212> PRT
<213> Homo sapiens

<400> 213

Lys Ala Thr Gln Lys His Ser Ser Thr Lys Trp Ser Ala Ser Asn Cys
1 5 10 15

Ser Val Ser Gly Phe Tyr Asp Ala Glu Phe Gly Ser Ile Glu Ser Thr
20 25 30

Val Ser Met Asp Cys Pro Asn Pro Ser Ser Lys Ile Val Asp Ile His
35 40 45



BNSDOCID <WO 0162924A2 I >

Gly Leu Ser Gln Val His Cys Phe Ile Tyr Leu Phe Ile Tyr Leu Ile
50 55 60

Leu Asp Ser Arg Ala His Val Gln Val Cys Tyr Met Asp Ile Leu Cys
65 70 75 80

Asp Ala Asp Val Trp Val Ser Ile Glu Pro Val Thr Leu Ile Val Asn
85 90 95

Leu Val Pro Asn Trp Asn Trp Met Gln Gly Leu Ser Arg Ser Arg Thr
100 105 110

Gly Ser Ser Pro Pro Asp Leu Leu Gly Leu Asp Leu Leu Lys Asp Gln
115 120 125

Lys Gly Arg Arg Tyr Glu Leu Asp Ala Cys Thr Gln Tyr Ser His Ser
130 135 140

Val Phe Glu Ala Tyr Leu Asp Gln Gly Cys Asp Leu Leu Lys Gly Ile
145 150 155 160

Thr Lys Ala Thr Thr Leu Ser Ala Asn Lys Val Val Ser Asn Leu Ile
165 170 175

Ile Ile His Phe Leu Leu Leu His Phe Lys Ile Asp Thr Cys
180 185 190

<210> 214
<211> 76
<212> PRT
<213> Homo sapiens

<400> 214

Thr Pro Ile Asp Ser Asp Leu Glu Val Arg Ala Lys Ala Tyr Pro Glu
1 5 10 15

Pro Pro Ser Leu Thr Pro Leu Phe Gln Phe Ser Phe Ser Gln Ile Ser
20 25 30

Pro Leu Gly Cys Ala Lys Pro Ser Trp Ile Gln Lys Phe His Phe Gln
35 40 45

Tyr Gly Tyr Cys Phe Gln Ser Ile Thr Pro Lys Asn Ser Arg Arg Lys
50 55 60

Lys Gly Ser Val Val Ile Phe Lys Ser Gln Asn His
65 70 75

<210> 215
<211> 169
<212> PRT
<213> Homo sapiens

<400> 215

Arg Asp Thr Ala Ile His Gly Val Phe Met Asn Leu Ser Leu Met Asn
1 5 10 15



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Ala Tyr Asp Met Phe Ile His Leu Phe Val Glu Ser Phe Asp Arg Phe
20 25 30

Ala Gln Asn Arg Glu Val Val Val Val Ala Val Trp Ile Trp Glu Gly
35 40 45

Glu Val Ser Phe Gly Gln Val Ile Ser Ala Tyr Gln Thr Ile Lys Gly
50 55 60

Ser Ala Phe Thr Glu Cys Trp Leu Gly Cys Asp Ser Cys Phe Ala Leu
65 70 75 80

His Ser Leu Lys Arg Leu Tyr Val Ser Pro Leu Cys Pro Phe Pro Ser
85 90 95

His Leu Lys Ile Asn Arg Arg Glu Asn Asn Val Ile Arg Gly Ser Asn
100 105 110

Cys Ile Tyr Cys Leu Cys Arg Val Val Val Asp Thr Gly Met Phe Pro
115 120 125

Tyr Ser Leu Cys Leu Ala His Leu Lys Cys Val Ile Ile Asn Asp Ile
130 135 140

Leu Lys Asn Thr Glu Gln Leu Val Leu Gly Ile Cys Pro Thr Ser Tyr
145 150 155 160

Asp Ser Ser Ala Ile Leu Ile Ser Leu
165

<210> 216
<211> 111
<212> PRT
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<400> 216

Lys Arg Ser Leu Asp Tyr Tyr Tyr Ile Ile Gln Met Cys Met Cys Val
1 5 10 15

Ser Ala Met Tyr Leu Leu Leu Leu Ser Arg Val Tyr Asn Met Lys Leu
20 25 30

Leu Thr Ile Ile Gln Glu Ile Arg Cys Met Asn Leu Val Gly Asn Val
35 40 45

Ser Tyr Tyr Asn Phe Tyr Asn Ile Ser Phe Lys His Phe Asp Ala Phe
50 55 60

Leu Leu Phe Lys Arg Leu Arg Asn Glu Asn Ile Lys Ile Asn Ile Phe
65 70 75 80

Leu Lys Cys Cys Ala Phe Tyr Leu Met Leu Leu Leu Ile Arg Ser Cys
85 90 95

Val Ile Leu Phe Leu Ile Glu Phe Asp Ile Arg Asn Lys Gly Arg
100 105 110



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<210> 217
<211> 180
<212> PRT
<213> Homo sapiens

<400> 217

Leu Thr Tyr Tyr Leu Gln Arg Asn Leu Ser Lys Pro Phe Leu Leu Tyr
1 5 10 15

Leu Ala Ser Arg Ile Pro Leu Pro Thr Phe Asn His Pro Gly Thr Leu
20 25 30

Tyr Thr Ser Ile Leu Thr Leu Phe Ile Leu Pro Phe Val Ile Ile Ala
35 40 45

Ser Cys Phe Arg Ala Pro Leu Asn Thr Lys Val Phe Glu Ser Arg Asn
50 55 60

Ser Lys His Phe Lys Phe Leu Ser Leu His Met Gln Leu Leu Leu His
65 70 75 80

Ser Gln Tyr Thr Val Asn Ala Asp Ile Glu Arg Ile Ser Leu Leu Glu
85 90 95

Cys Asn Ser Leu Arg Val Ser Asn Ser Ser Ser Leu Lys Thr Asn Pro
100 105 110

Thr Lys Leu Thr Ile Val Ser Thr Thr Lys Ser Leu Gln Val Ile Asn
115 120 125

Leu Thr Ile Glu Val Phe Ile Phe Leu Leu Gly Lys Pro Gly Gln Pro
130 135 140

Gln Gly Pro Thr Tyr Pro Gly Val Thr Leu Lys Val Met Arg Phe Pro
145 150 155 160

Ser Lys Met Thr Lys Leu Ser Gly Phe Ser Gly Met His Thr His Cys
165 170 175

Val Thr Ile Asn
180

<210> 218
<211> 219
<212> PRT
<213> Homo sapiens

<400> 218

His Ile Glu Cys Ala Ile Pro Ser Asn Phe Cys Phe Asn Asn Cys Lys
1 5 10 15

His Ile Phe Cys Lys Tyr Asn Phe Ala Ser Arg Ala Ile Cys Phe Thr
20 25 30

Ser Leu Ile Ile Phe Cys Tyr Thr Asp Leu Gln Val Ile Leu His Lys
35 40 45



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Val Gly Leu Asn Leu Lys Cys Leu Leu Phe Ile Lys Cys Cys Pro Leu
50 55 60

Leu Met Phe Ile Ile Tyr Ile Phe Leu Val Leu Asn Leu Asp Trp Lys
65 70 75 80

Asn Met Leu Cys Lys Ile His Gly Asn Ile Phe Arg Thr Asn Phe Tyr
85 90 95

Leu Tyr Arg Trp Leu Ile Ser Cys Ser Glu Asn Lys Thr Met Asn Lys
100 105 110

Gln Cys Phe Ile Tyr Ser Ser Phe Asn Val Ser Gln Val Asn Thr Tyr
115 120 125

Leu Leu Tyr Phe Leu Ser Ala Val Thr Pro Pro Phe Leu Leu Phe Ser
130 135 140

Ser Val Trp Leu Cys Pro Arg Ala Asn Ser Val Pro Ser Ile Arg Leu
145 150 155 160

Ser Val Tyr Ser Thr His Gly Leu Glu Leu Lys Trp Leu Gly Asn Cys
165 170 175

Asn Thr Val Asp Trp Ser His Phe Lys Leu Ala Gln Thr Trp Ser Tyr
180 185 190

Cys Ile Pro Lys Met Asn Ser Leu Ile Arg Thr Thr Phe Pro Thr Phe
195 200 205

Ser Cys Leu Leu Lys Pro Pro Ser Pro Leu Pro
210 215

<210> 219
<211> 211
<212> PRT
<213> Homo sapiens

<400> 219

Phe Val Leu Cys Ile Phe Ser Leu Gly Ser Val Ser Val Ser Ser Pro
1 5 10 15

Cys Asn Lys Leu Ser Gln Val Ser Cys Phe Gln Val Phe Val Phe Leu
20 25 30

Val Asn Tyr Gln Thr Arg Gly Phe Gly Glu Leu Leu Glu Phe Ala Ile
35 40 45

Gly Val Arg Ser Glu Asp Asn Leu Val Cys Thr Val Phe Ser Leu Thr
50 55 60

Leu Trp Gly Leu Gly Met Val Gly Gly Arg Glu Ser Arg Cys Val Lys
65 70 75 80

Leu Thr Val Ile Phe Leu Pro Lys Lys Lys Leu Ser Pro Gln Gly Tyr
85 90 95

Lys Glu Ala Thr Thr Val Phe Pro Thr Leu His Thr Lys Phe Gln Gln



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                100                     105                     110

Trp Asn Phe Met Ile Tyr Leu Gly Asn Tyr Ile Trp Arg Asn Val Leu
        115                     120                     125

Lys Leu Gln Ile Leu Thr Lys Asp Phe Leu Lys Tyr Ser Asn Lys Val
    130                     135                     140

Ile Asp Cys Asn Gln Asn Ser His Leu Pro Lys Arg Arg Trp Tyr Ser
145                     150                     155                     160

Ile Leu Lys Val Ile Ile Leu Leu Gly Lys Gln Cys Leu Pro Val Leu
                165                     170                     175

Ile Ile Ile Leu Glu Thr Thr Val Phe Ile Asn Val Ser Glu Ile Tyr
            180                     185                     190

Asn Leu Asn Glu Ile Leu Met Pro Lys Met Asn Thr Gly His Ile Phe
        195                     200                     205

Lys His Tyr
    210

<210>  220
<211>  177
<212>  PRT
<213>  Homo sapiens

<400>  220

Ile Leu Lys Ile Ile Ser Leu Asp Thr Val Leu Leu Cys Val Ser Tyr
1               5                   10                  15

Arg Ser Thr Ile Val Phe Ser Leu Phe Pro Ile Val Ile Arg Asp Arg
            20                  25                  30

Ser Ser Ser Leu Phe Phe Leu Leu Gln Ser Phe Ile Trp Asn Leu Phe
        35                  40                  45

Trp Cys Leu Ile His Lys Tyr Leu Ile Cys Leu Pro Asn Arg Val Lys
    50                  55                  60

Met Ile Pro Val Met Leu Leu Ile Cys Val Leu Arg Arg Lys Lys Ser
65                  70                  75                  80

Gly Ser Thr Met Ala Leu Gly Ile Leu His Lys Pro Met Lys Ala Val
                85                  90                  95

Thr Phe Val Asn Val Phe Leu Val Glu Thr Ser Val Glu Asn His Cys
            100                 105                 110

Cys Ile Ile Val Leu Ser Ser Arg Thr Tyr Ser Gly Asp Gly Asn Thr
        115                 120                 125

Leu Leu Tyr Phe Pro Ile Trp Tyr Ser Leu Thr Thr Cys Gly Tyr Gln
    130                 135                 140

Val Leu Glu Met Trp Leu Gly Asp Gly Thr Glu Ile Phe Ser Leu Ile
145                 150                 155                 160
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Leu Ser Val Ile Tyr Thr Thr Ala Tyr Phe Ile Glu Ser Thr Phe Ser
                165                 170                 175

Ile
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